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# Impact of Intensity and Body Temperature

# on Cardiovascular Responses to Exercise

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# Impact of Intensity and Body Temperature

# on Cardiovascular Responses to Exercise

by

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## DEDICATION

To my wife, Timi, my daughter, Sadie, and my family, without their support I would not be where I am today.

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I would first like to thank Dr. Edward Coyle for his guidance and mentoring over the last 7 years. The training that I have received under his supervision has allowed me to become a confident and independent investigator in the field of Exercise Physiology. Thank you for always reminding me to ask the question, “What is the question?” Next I would like to thank Matthew Pahnke for being the only lab mate that has been with me through the entirety of my time here at The University of Texas. Working in the lab was quite different when it was just the two of us. Thank you for your friendship over this time and thank you for all the help that you gave in forming, implementing, and carrying out my research studies. Next I would like to thank Justin Trombold for his unending desire to discuss research and for always wanting to expand his knowledge of physiology. I would also like to thank Joshua Lee for his technical assistance and participation in numerous pilot studies and his desire to learn and take an active part in the lab. Without the assistance of the following people my research would never have been accomplished; Il-Young Kim, Lisa Stegall, Mike Casner, Sara Eubanks, Ari Reinfeld, Jim Casler, Sang-he Park, Moses Kahn, and Megan Cannon. I would also like to thank Dr. Ken Beck for his guidance, feedback, and technical assistance over the course of the last two years. Thank you to Patty Coffman and Mina Rathbun for your behind the scenes work and support. Most importantly, a huge thank you to my wife Timi Trinity. Your support, prayers, and love over the last 7 years have been unending and for this I am forever grateful.

# Impact of Intensity and Body Temperature on Cardiovascular Responses to Exercise

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These studies investigated the impact of intensity and body temperature on performance and cardiovascular regulation during high intensity and prolonged exercise. In study 1, polyphenol antioxidant supplementation proved to have no effect on exercise performance and related variables (gross efficiency, perceived exertion, maximal power) during exercise in the heat. Furthermore, there were no differences between the cardiovascular or thermoregulatory responses between control and antioxidant treatments. Study 2 utilized an integrative approach to investigate a classic topic in exercise physiology, namely, is the cardiac output to oxygen consumption relationship linear across a wide range of exercise intensities? The slope of the CO vs. VO2 relationship was significantly reduced from 70 to 100% of VO2max when compared to the slope from 40 to 70% of VO2max (2.0 ± 0.4 vs. 4.4 ± 0.3 l/min, p = 0.025). This finding, in combination with the plateau and eventual reduction in stroke volume at high intensity exercise compared to moderate intensity exercise (146.0 ± 16.6 vs. 138.5 ± 14.9 ml/beat, p = 0.015), argues in favor of a cardiac limitation to high intensity

exercise. This study also showed that the pattern of oxygen extraction at the whole body level (arterial venous O2 difference) and the muscle level (deoxygenated hemoglobin) is not similar and that muscle specific differences exist regarding oxygen extraction. Study 3 determined that hyperthermia (elevation of skin temperature by 4.3$^{o}$C and core temperature by 0.8$^{o}$C) did not reduce SV independent of the increase in HR. Even under conditions of moderate hyperthermia the reduction in SV is due to the increase in HR and temporally unrelated to increases in cutaneous blood flow. In summary, antioxidant supplementation had no effect on performance, cardiovascular, or thermoregulatory responses to exercise in the heat in well trained subjects. High intensity exercise is associated with a reduced rate of increase in the CO vs. VO2 relationship. Finally, hyperthermia does not reduce SV during exercise when HR is maintained at normal levels.

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# CHAPTER 1: INTRODUCTION

During exercise the cardiovascular system is responsible for delivering oxygenated blood to the active muscle in order to meet the energetic demands of muscular activity. Similarly, during passive heating a severe strain, second only to exercise, is placed on the cardiovascular system as blood is directed from central to peripheral sites in an attempt to maintain thermal homeostasis (Rowell *et al.*, 1969a; Rowell *et al.*, 1969c; Johnson & DW, 1996; Crandall, 2008). Blood flow to active muscle and skin is ultimately limited by cardiac output (CO) as CO cannot continue to increase without end. Mean arterial blood pressure must be maintained in order to perfuse critical tissues such as the brain and heart. During maximal small muscle exercise, blood flow to active muscle can be as high as 250 to 400 ml/100g/min (Richardson *et al.*, 1993; Saltin *et al.*, 1998). Total skin blood flow, second only to skeletal muscle in terms of vasodilation capacity, can increase to as high as 8 l/min under severe heat stress (Rowell *et al.*, 1969a). If muscle and skin were to maximally vasodilate, CO would have to exceed 50 l/min. Most endurance trained athletes possess a CO in the 25 to 30 l/min range with a few elite individuals reaching a CO of 35 to 40 l/min (Ekblom & Hermansen, 1968). A reduction in muscle blood flow will limit the intensity and duration of exercise, whereas a reduction in skin blood flow will reduce heat dissipation, both of which are intimately linked to exercise tolerance and fatigue (Gonzalez-Alonso *et al.*, 2008).

## CHAPTER II: STATEMENT OF THE PROBLEM

Study 1 focused on antioxidant supplementation and exercise performance in the heat. The specific aims of study 1 were:

1. Determine if exercise performance in the heat is improved by antioxidant supplementation.
2. If exercise performance is improved, is this improvement related to a reduction in cardiovascular strain and improved thermoregulatory control during exercise?

Study 2 examined the cardiac output and stroke volume responses to high intensity exercise. The specific aims of study 2 were:

1. Use a series of steady state intervals to determine if the cardiac output to VO2 relationship is linear across a wide range of exercise intensities.
2. To investigate the SV response to high intensity exercise.
3. Compare central (cardiac output, stroke volume, heart rate, arterial venous O2 difference) and peripheral cardiovascular responses (deoxygenated hemoglobin) from moderate to high intensity exercise.

Study 3 focused on the independent effect of hyperthermia on the stroke volume response to moderate intensity exercise. The specific aims of study 3 were:

1. Use a low dose of cardio-selective beta blockade (atenolol) to determine the effect of hyperthermia on SV independent of HR.
2. Determine if the reduction in SV during prolonged exercise in the heat is temporally unrelated to increases in peripheral blood flow.

## CHAPTER III: EXPERIMENTAL DESIGN

**Study 1:** A placebo controlled randomized cross over design was used to determine if antioxidant supplementation improved exercise performance in the heat. Twelve well trained endurance athletes consumed twice daily supplements of either placebo or polyphenol antioxidant (POM) for one week. On day 6 of supplementation subjects performed a one hour bout of exercise in the heat (31.5$^{o}$C, 55% RH) which included determination of gross cycling efficiency, 30 minutes of cycling at 5% below lactate threshold, and a 10 minute time trial. During exercise measures of cardiovascular responses (HR, SV, CO, BP) and body temperatures (core and skin) were made. On day 7 subjects returned to the laboratory and exercised in the heat at VO2max until exhaustion during which cardiovascular and body temperature measurements were made. Near infrared spectroscopy (NIRS) was used in a subset of subjects (n=5) to determine if the antioxidant treatment had any effect on muscle oxygenation / deoxygenation status during exercise.

**Study 2:** This experiment focused on cardiovascular responses to high intensity exercise. Ten well trained cyclists performed a series of preliminary tests (incremental and discontinuous VO2max tests) to determine the minimal workrate needed to attain VO2max. Following these preliminary tests interval cycling was performed. The intervals included exercise bouts at 40, 50, 60, 70, 80, 90 and 100% of VO2max. Cardiac output and stroke volume were measured during each interval and the CO vs. VO2

relationship and the SV response was established across a full range of exercise intensities. Near infrared spectroscopy (NIRS) was used to determine the deoxygenation status of the vastus lateralis and the gastrocnemius.

**Study 3:** In order to determine the effect of hyperthermia on SV independent of HR, eleven moderately trained subjects performed 1 hour of moderate intensity exercise (57% VO2max) under four experimental conditions; normothermia and placebo (NormoPL), normothermia and beta blockade (Normo βB), hyperthermia and placebo (HyperPL), and hyperthermia and beta blockade (Hyper βB). Hyperthermic conditions resulted in higher core and skin temperatures (0.8$^{o}$C and 4.3$^{o}$C, respectively). In order to prevent the normal increase in HR during exercise a low dose (0.2mg/kg) of the β1 cardioselective beta blocker atenolol was ingested immediately prior to exercise. Beta blockade resulted in a nearly identical HR response for the NormoPL and Hyper βB thereby allowing for a direct comparison of SV under conditions of hyperthermia independent of HR.

## CHAPTER IV: STUDY 1

## EFFECT OF POLYPHENOL SUPPLEMENTATION ON PERFORMANCE AND CARDIOVASCULAR RESPONSES TO EXERCISE IN THE HEAT

**Abstract:**

Dietary supplementation with antioxidants has gained popularity in recent years; however, the effects of antioxidants on exercise performance in the heat have not been well described. The purpose of this study was to determine if supplementation with polyphenol antioxidants (POM) improves exercise performance in the heat (31.5$^{o}$C, 55% RH) by altering the cardiovascular and thermoregulatory responses to exercise. Near infrared spectroscopy was measured in a subset of subjects (n = 5) to determine if POMS had any effect on muscle oxygenation and deoxygenation. Twelve well trained endurance athletes ingested POM or placebo (PLA) for 7 days. Consecutive days of exercise testing were performed at the end of the supplementation periods (i.e.; Day-1 and Day-2 of testing). Performance during a 10 minute time trial (TT) on Day-1 was not different between treatments (PLA; 292 ± 33 W and POM; 279 ± 38 W, p = 0.12). Similarly, gross efficiency (GE), blood lactate (La), maximal neuromuscular power (Pmax), and ratings of perceived exertion (RPE) were not different between treatments. Furthermore, time to fatigue at VO2max on Day-2 was not different between treatments (PLA; 377 ± 117 sec vs. POM; 364 ± 128 sec, p = 0.61). The overall cardiovascular and thermoregulatory responses to exercise were not different between treatments on either day of exercise testing. In conclusion, antioxidant supplementation

did not alter the cardiovascular or thermoregulatory response to exercise and performance in the heat was not improved.

**Introduction:**

High intensity exhaustive exercise is associated with an increase in oxidative stress and free radical production (Davies *et al.*, 1982; Bailey *et al.*, 2004; Powers & Jackson, 2008). Furthermore, heat stress during exercise has also been shown to exacerbate the increase in oxidative stress during exercise (Flanagan *et al.*, 1998; McAnulty *et al.*, 2005). Therefore, the combination of exhaustive exercise and heat stress yields an ideal situation to test if antioxidant supplementation can improve exercise performance. To date, the results from experiments using antioxidants are equivocal as some investigators have found an increase (Medved *et al.*, 2004a; Medved *et al.*, 2004b; MacRae & Mefferd, 2006; McKenna *et al.*, 2006; McKenna *et al.*, 2008; McKenna & Hargreaves, 2008; Davis *et al.*, 2009), no change (Cheuvront *et al.*, 2009; Nieman *et al.*, 2009; Utter *et al.*, 2009), or decrease in performance (Gomez-Cabrera *et al.*, 2008).

Rather compelling evidence for the beneficial role of antioxidant supplementation and exercise performance has been shown with intravenous infusion of the free radical scavenger n-acetylcysteince (NAC) (Travaline *et al.*, 1997; Bailey *et al.*, 2004; Medved *et al.*, 2004a; Medved *et al.*, 2004b; Matuszczak *et al.*, 2005; McKenna *et al.*, 2006; McKenna *et al.*, 2008; McKenna & Hargreaves, 2008). NAC has been shown to delay fatigue during high intensity exercise by improving antioxidant status and ion (K+) regulation (Bailey *et al.*, 2004; Medved *et al.*, 2004a; Medved *et al.*, 2004b; McKenna *et al.*, 2006). However, these studies used supraphysiological dosages of the antioxidant

and administered the dose via intravenous infusion. Contrary to these findings, most studies using oral administration of quercetin (a polyphenol antioxidant) have found no beneficial effect on exercise performance (Cheuvront *et al.*, 2009; Nieman *et al.*, 2009; Utter *et al.*, 2009) while only one study in humans has shown improved exercise performance with oral quercetin ingestion (MacRae & Mefferd, 2006). Further investigation is required to determine if physiological dosages of antioxidants increase performance in healthy individuals.

The antioxidant supplement used for this study is a mixture of high potency polyphenols found in pomegranate juice (POM). Previous work has shown POM to possess higher antioxidant potency when compared to other polyphenol rich fruits and pharmacokinetic analysis revealed that plasma levels of the active antioxidants peak 1 to 2 hours after consumption and are present in the urine for 48 hours (Seeram *et al.*, 2006; Seeram *et al.*, 2008a; Seeram *et al.*, 2008b). Furthermore, POM has been shown to increase nitric oxide (NO) bioavailability by protecting the molecule from oxidative destruction (Ignarro *et al.*, 2006). Given the important roles of NO in cutaneous blood flow (Kellogg *et al.*, 1998), thermoregulatory control of sweating (Welch *et al.*, 2009), and skeletal muscle blood flow (Boushel *et al.*, 2002; Mortensen *et al.*, 2007), we thought POM would be an ideal antioxidant supplement to test for ergogenic properties during exercise.

The primary purpose of this study is to determine if POM supplementation improves exercise performance in the heat. We hypothesized that POM would increase performance in the heat and that this increase in performance would be associated with reduced cardiovascular strain and improved thermoregulation during exercise. Secondly, by performing exhaustive exercise on consecutive days, we were able to test if POM supplementation aided in recovery from one day to the next.

**Methods:**

*Subjects:* Twelve healthy and well trained male cyclists (26.8 ± 5.0 yr of age) provided written informed consent to participate in this study. The protocol, experimental design, and informed consent were approved by the Institutional Review Board at The University of Texas at Austin. The subjects' stature, body mass, and maximal oxygen consumption (VO2max) (means ± SD) were as follows: 1.80 ± 0.08 m, 74.4 ± 8.8 kg, 4.459 ± 0.305 l/min, respectively.

*Experimental design*: A double blind placebo controlled randomized cross over design consisting of two testing periods each lasting seven days was utilized. During each of the testing periods subjects performed exercise tests on days six and seven of supplementation or placebo control (Day-1 and Day-2 of testing, respectively). Consecutive (back-to-back) days of testing allowed us to determine whether or not supplementation with POM aided in recovery from exhaustive exercise performed on the previous day. In order to match diet from one treatment to the next subjects kept dietary logs for days four, five, and six and an overnight fast of at least 10 hours was performed prior to testing on days six and seven (i.e.; Day-1 and Day-2). All testing was performed at the same time of day. Prior to the start of the experimental trials subjects reported to the laboratory on three separate occasions to perform preliminary and familiarization testing.

*Experimental protocol:* Preliminary and familiarization testing was performed over the course of three visits to the laboratory (Sessions 1, 2, and 3). Session 1 included a submaximal exercise test on a cycle ergometer (Excalibur Sport, Lode, Groningen, The Netherlands) to determine lactate threshold and oxygen cost of loaded cycling and an incremental test to exhaustion to determine VO2max. Position on the ergometer was matched to the subject's road bicycle and kept constant throughout the study. The submaximal test included 5 stages each lasting 5 minutes. Workrate was progressively increased by 20 to 40 watts depending on the fitness level of the subject. Lactate samples were collected during the final minute of each stage by a finger stick and analyzed with a portable lactate meter (Lactate Pro, Arkray Inc, Kyoto, Japan). Lactate threshold (LT) was determined as the 1 mmol increase above baseline. Oxygen consumption (VO2) was collected continuously during this test. VO2 data was averaged over the final minute of each stage to determine the oxygen of cost of cycling at each workrate. Following the submaximal test subjects rested for 10 minutes before performing an incremental VO2max test, which lasted 8 to 12 minutes. Initial workrate for the VO2max test was set at a workrate that elicited approximately 80% of subject's reported maximal heart rate (HRmax). Session 1 was performed in the environmental chamber under moderate temperature conditions (24$^{o}$C and 50% relative humidity (RH)).

Familiarization sessions 2 and 3 were performed on consecutive days. The protocol for familiarization and experimental trials was identical and the experimental

timeline is described in Figures 1A and 1B. The purpose of the familiarization trials was twofold; first, acquaint subjects with the testing procedures and the demands of the exercise tests, and second, determine the appropriateness of the workrates for each of the exercise tests. Upon arrival at the laboratory subjects were asked to void their bladder and obtain a nude bodyweight (Lifesource UC-321 precision scale, Lifesource). Nude bodyweight was also obtained after exercise. Subjects then inserted a rectal temperature probe (model 401, Yellow Springs Instrument) 12 cm past the anal sphincter. Subjects were then instrumented and escorted to the environmental chamber and asked to sit quietly on the ergometer for 5 minutes while resting blood pressure measurements were made (STBP-680, Colins). Subjects then performed a 5 minute warm-up at 60% of their VO2max. Immediately following the warm-up subjects exited the environmental chamber and performed 4 maximal power sprint tests on an inertial load ergometer. After the maximal power tests subjects reentered the environmental chamber and began the 1 hour bout of exercise. During the first 20 minutes of the 1 hour test subjects cycled at 40, 50, 60, and 70% of VO2max for 5 minutes for the determination of gross cycling efficiency (APPENDIX A). At minute 20 workrate was adjusted to 5% below LT. At minute 50 a 10 minute time trial (TT) began. The TT began at a workrate that would elicit approximately 90% of VO2max. After the first 2 minutes of the TT the subject was able to change the workrate every 30 seconds. The power output was changed by a member of the research team as instructed by the subject. Verbal encouragement was given to the subject by a designated member of the

research team. The goal of the TT was to perform as much work as possible during the 10 minute period. A similar protocol has been successfully used by our lab (Below *et al.*, 1995).

On Day-2 of the experimental testing (and familiarization session 3) subjects performed the same warm-up and series of maximal power tests as previously described (Figure 1B). After completion of the maximal power test subjects entered the environmental chamber and began a 10 minute exercise bout which consisted of 5 minutes of cycling at 60% and 5 minutes at 70% of VO2max. At min 10 an open-ended ride to fatigue began. Workrate for this performance test was set so as to elicit 100% of VO2max. Previous work from our lab has shown that well trained endurance athletes were able to cycle for 5 to 9 min at this workrate (Dingwell *et al.*, 2008). Subjects were verbally encouraged to give a maximal effort during all trials. All trials except session 1 (preliminary submaximal and VO2max tests) were performed in the environmental chamber under warm conditions (dry bulb temperature: 31.5$^{o}$C, RH: 55.1%)

*Supplementation:* Supplements of POM or PLA (500 mL) were taken twice daily at 12 hour increments over the seven-day testing period. On day 6 (Day-1 of testing) and day 7 (Day-2 of testing), subjects consumed the supplement approximately 30 minutes before the start of the exercise test. POM and PLA drinks were provided by POM Wonderful, LLC (Los Angeles, CA). Products were shipped frozen and were stored at 4°C upon arrival. Each bottle of POM contained 1800-ppm polyphenols, comprised of

95.5% eligatanins (22.5% as punicalins and punicaligans), 3.5% ellagic acid, and 1% anthocyanins. Both POM and PLA contained a very low amount of carbohydrate (4 grams maltodextrin and sucralose) with additional coloring and flavoring to blind the treatments. Subjects were reminded verbally and through e-mail communication to consume the experimental supplements at the required times.

*Respiratory measurements:* Oxygen consumption was determined using a commercially available metabolic cart (Max II Modular Metabolic System, AEI Technologies, Pittsburg, PA) while subjects cycled on an electromagnetically braked ergometer. Gas analysis was performed using oxygen and carbon dioxide analyzers (Applied Electrochemistry, Models S-3A/I and CD-3A, respectively) while the subjects breathed through a one-way valve (Hans Rudolph, Kansas City, MO). Ventilation was measured with an inspiratory pneumotachometer (Hans Rudolph, Kansas City, MO).

*Cardiovascular measurements:* An impedance cardiography device (Physioflow Type PF05L1, Manatec Biomedical, Macheren, France) was used to measure heart rate (HR), stroke volume (SV), and cardiac output (CO). The Physioflow unit uses changes in transthoracic impedance (dZ) in response to an administered electrical current during cardiac ejection to calculate SV. The Physioflow emits a high frequency (75 kHz) and very low-amperage (3.8 mA peak-to-peak) alternating electrical current via skin electrodes (Series 810 electrodes, S&W Healthcare). Two pairs of electrodes, one transmitting and the other receiving, were applied above one another so as to not overlap at the supra-

clavicular fossa at the left base of the neck and at the midpoint of the thoracic region of the spine. An additional pair of electrodes was used to monitor a single ECG lead (V1/V6 position). The physioflow impedance cardiograph has been validated against the direct Fick method (Charloux *et al.*, 2000) and mean differences between CO as measured by the direct Fick and the physioflow were not found to be significantly different at rest, during submaximal exercise, or during incremental maximal exercise (Richard *et al.*, 2001). Prior to placement of electrodes, the skin was cleaned with isopropyl alcohol and a gauze sponge. Subjects wore a spandage® shirt around their torso and coban® tape around their neck to reduce movement of electrode wires and to insure that electrodes were kept in place throughout the duration of the exercise tests.

Blood pressure (BP) was collected using an automated blood pressure device (STBP-680, Colins). Resting measurements were made while the subject sat quietly on the cycle ergometer with their right arm relaxed on the handlebars of the ergometer. During the 1 hour exercise bout of Day-1 BP was measured with the subject's arm relaxed on the handlebars during the final minute of each submaximal stage, at min 30 and 45, and again at two minute intervals during the 10 min TT.

*Body temperatures and rating of perceived exertion:* Core temperature (Tcore) was measured using a rectal temperature probe inserted 12 cm past the anal sphincter. Skin Temperature (Tskin) was measured using skin thermistors (model 409A, Yellow Springs Instrument) at six sites; back, chest, bicep, forearm, thigh and calf and mean

Tskin was calculated based on the equation of Hardy and Dubios (Hardy *et al.*, 1938). Body temperature (Tbody) was calculated using the equation of Baum et al. (Baum *et al.*, 1976) (Tbody = .87*Tcore + .13*Tskin). All temperature data was collected continuously on a personal computer using Tracer-Daq (Measurement Computing) software interfaced with an A/D board (USB Temp, Measurement Computing). Ratings of perceived exertion (RPE) were collected using the Borg 6 to 20 point scale (Borg, 1975) at min 30 and 45 of the one hour exercise bout on Day-1.

*Near Infrared Spectroscopy:* Muscle oxygenation was determined by a frequency-domain multi-distance NIRS system (Oxiplex TS, ISS, Champaign, IL) in a subset of subjects (n = 5). The principles of operation and algorithms used by this NIRS system have been previously described (Gratton *et al.*, 1997). For this experiment the NIRS probe was positioned longitudinally on the belly of the vastus lateralis approximately 12 cm above the lateral border of the patella. The probe was held in place by a Velcro strap provided by the manufacturer and the subject's cycling shorts were pulled over the probe to minimize movement of the probe. The NIRS system was calibrated prior to each test after a warm-up of at least 30min. The calibration was done with the optical probe placed on the calibration block with absorption and reduced scattering coefficients previously measured and correction factors were determined and automatically implemented by the equipment's software for the calculation of the absorption coefficient (μa) and reduced scattering coefficient (μs) for each wavelength during the data collection. The NIRS system provides a continuous measurement of

absolute concentration of oxyhemoglobin (HbO) and deoxyhemoglobin (HHb) (expressed in μM). The HHb reported in the present study was calculated incorporating the continuous measurement of μs made throughout the exercise test, i.e.; without assuming a constant for scattering. All NIRS data was averaged over 30 seconds.

*Maximal neuromuscular power:* Maximal neuromuscular power (Pmax) was determined by the inertial load ergometry. Validation and reliability of the inertial load has been previously described in detail (Martin *et al.*, 1997). Briefly, the inertial load ergometer uses the resistance created by the moment of inertia of a flywheel to represent the force that the subject accelerates during the test. Power is calculated as the product of inertia, angular velocity and angular acceleration. Flywheel angular velocity and acceleration are determined by an optical sensor and micro-controller based computer interface which measures time (± 0.5 microsecond) and allows power to be calculated instantaneously every 3 degrees of pedal crank revolution and averaged over one complete revolution of the pedal cranks (Pmax). The coefficient of variability with this technique is ± 2.5% and this high degree of reliability has allowed mean treatment differences in maximal power of 2-3% within a population to become statistically significant (Trinity *et al.*, 2006; Trinity *et al.*, 2008). The measurement of Pmax requires maximal effort over 2 to 3 seconds with 60 seconds of passive recovery between efforts. Subjects performed familiarization with the inertial load ergometer during sessions 2 and 3. Four measures of Pmax were collected during day 1 of the

experimental trials. All Pmax values were obtained after a 5 minute warm-up and prior to the prolonged exercise tests.

*Statistics:* All statistical analyses were performed using SPSS version 14.0. Data are presented as mean ± standard deviation of the mean. For the purpose of clarity data presented in figures is presented as mean ± standard error. A two-way (trial x time) repeated measures ANOVA analyses was used to test for significant differences. A priori analyses of sequential time points was employed following a significant main effect of time. The number of a priori comparisons was limited to k-1 for each variable measured, where k is equal to the number of means compared. If the interaction (treatment x time) was found to be significant, pairwise comparisons were made using a paired samples T-test. If Mauchly's test of sphericity was violated, the Greenhouse-Geisser correction was used to correct for this violation. Average power during the TT (D-1) and time to fatigue (D-2) were analyzed using a paired samples T-test. For statistical analysis data from Day-1 was separated into two groups; data from rest to 50 minutes of exercise and data during the 10 min TT. Significance was accepted at the $P < 0.05$ level.

**Results:**

**DAY - 1:**

*Subject characteristics and environmental factors:* BW prior to exercise was not different for both treatments (Table 1.1). BW post exercise was similar indicating that the reduction in BW was not different for both treatments. The reduction in BW from pre to post exercise (PLA; -0.7% and POMS; -0.6%) was significant ($p < 0.01$); however, dehydration of less than 1% is minor and not expected to be a confounding variable in the study.

Dry bulb temperature (DB), black globe temperature (BG), and relative humidity (RH), were held constant over the course of each trial and no differences existed between trials. DB averaged 31.5 ± 0.7$^{o}$C while BG averaged 31.6 ± 0.5$^{o}$C with an average RH of 55.1 ± 3.7%.

*Exercise intensity and respiratory responses:* Actual exercise intensity during the first 50 minutes of exercise is reported in Table 1.2. During the first 20 minutes of exercise subjects cycled at workrates that elicited 41, 53, 63, and 74% of VO2max. VO2 increased to the same extent at each of the 4 stages for both treatments indicating that GE was not influenced by the POMS supplementation (Table 1.2). GE increased as workrate increased with the highest GE occurring at approximately 74% of VO2max. From minute 20 to 50, workrate was adjusted to 5% below lactate threshold which corresponded to 229 ± 17W.

*Exercise performance:* There was no difference in average power output during the 10 minute TT. Subjects averaged 292 ± 33 W and 279 ± 38 W ($p = 0.12$) for the PLA and POMS trials, respectively (Figure 1.2). Workload, when divided into quartiles (2.5 minute periods), was not different between trials at any time point (Table 1.3). Workrate was significantly reduced from the first to second quartile of the TT and continued to fall from the second to third quartile for both PLA and POMS. Workrate significantly increased during the final quartile during POMS but not during PLA. However, despite this end spurt during the POMS trial, average workrate during the last 2.5 minutes of the TT was not different between the trials. Lactate levels at minutes 5, 30, and post TT were not different between trials, similarly RPE was not different between trials (Table 1.4).

Measures of maximal power (Pmax), instantaneous power (IP), and velocity at maximal power (RPM) were not different between day-1 and day-2 or between treatments (Table 1.5).

*Thermoregulatory responses:* There were no pairwise differences between treatments for Tcore, Tskin, or Tbody during the one hour bout of exercise. Tcore increased with each increase in workload during the first 20 minutes of exercise and continued to increase from minute 20 to 50 as well as during the 10 minute TT reaching a peak value at the end of the TT (PLA; 38.90 ± 0.34$^{o}$C and POMS; 38.87 ± 0.28$^{o}$C). The only significant difference for Tcore between POMS and PLA was that the increase from

minute 20 to 50 was slightly higher for POMS than PLA (PLA; 0.64$^{o}$C [rate = 0.021$^{o}$C/min] vs. POMS; 0.74$^{o}$C [rate = 0.025$^{o}$C/min], $p < 0.01$) (Table 1.6). Tskin was slightly higher prior to exercise during the POMS trials; however, by minute 5 of exercise this difference was abolished. Tskin was maintained between 32.0 and 32.3$^{o}$C from minute 5 to minute 20 and reduced by 1.1$^{o}$C (PLA) and 0.8$^{o}$C (POMS) from minute 20 to minute 50 ($p < 0.05$). Similar to Tcore, the increase in Tbody from minute 20 to 50 was greater for POMS than PLA (PLA; 0.41$^{o}$C vs. POMS; 0.54$^{o}$C, $p < 0.01$). Overall, there were no pairwise differences between trials at any time point *during exercise* for Tcore, Tbody, and Tskin. However, the increase in Tcore and Tbody from minute 20 to minute 50 was significantly greater during POMS than PLA.

*Cardiovascular responses:* The HR response to the first 50 minutes of exercise was similar for PLA and POMS (Figure 1.4). Significant HR drift of 9 bpm (PLA; 5.6%, $p < 0.01$) and 11 bpm (POMS; 7.4%, $p < 0.01$) occurred from minute 20 to 50. HR increased to the same extent during the TT for both treatments (Figure 1.4). Due to the slightly lower (non-significant) power output during the POMS trial the overall treatment by time interaction for HR was significant during the TT; however, there were no pairwise difference between the treatments. The SV response to exercise was similar for PLA and POMS (Table 1.6). SV plateaued between 60 and 70% of VO2max, furthermore SV was not significantly increased during the TT despite increases in HR and CO. As with HR and SV, CO was not different between treatments (Table 1.6). CO increased by 1 to 1.5 l/min during the 20 to 50 minute period of exercise. During the TT CO increased from minute

50 and peaked at minute 58 and minute 60 for PLA (23.5 ± 3.8l/min) and POMS (23.6 ± 4.1l/min), respectively.

There were no differences between trials for SBP, DBP, and MABP (Table 1.6). SBP increased with each increase in exercise intensity and peaked at minute 20. SBP was maintained between minute 20 and 50 and increased during the TT, reaching peak values at minute 58 and 60 for PLA and POMS, respectively. DBP was reduced over the course of the first 20 minutes of exercise and reached a minimum at minute 20. DBP gradually increased from minute 20 to minute 50, and overall (effect of time independent of treatment) this increase was significant ($p = 0.003$). MABP increased with exercise and reached a peak value at minute 50. MABP was not different from minute 20 to minute 50. SVR was reduced by 50% with the onset of exercise and continued to decrease as exercise intensity increased.

Overall, no differences between treatments were observed for any CV related variable. HR and CO increased linearly as exercise intensity increased. Significant HR drift occurred between minute 20 and minute 50. This HR drift was accompanied by an increase in CO; however, SV, MABP, and SVR were all maintained during this period.

*NIRS and muscle oxygenation:* There were no differences between PLA and POMS for any of the NIRS related variables (Table 1.7). OxSat was reduced by 11.5% (PLA) and 7.6% (POMS) from minute 5 to 20 and continued to decline by 5% during the TT. THC increased during the first 50 minutes of exercise but did not change during the

TT. HbO showed no change during the first 50 minutes of exercise but was reduced by 5% (POMS) and 6% (PLA) during the TT. HHb increased 19.7% and 21.5% from 41 to 74% of VO2max for PLA and POMS, respectively and continued to increase by 7% (PLA) and 7.5% (POMS) during the TT.

**DAY - 2:**

*Exercise performance and respiratory responses:* During the fatigue test subjects cycled at a constant workrate of 338 ± 27 W. There was no difference in time to fatigue between the two treatments (PLA; 377 ± 117 sec vs. POM; 364 ± 128 sec, p = .61) (Figure 1.3). Based on the design of the study (i.e.; back to back days of exhausting exercise) we were able to ascertain that the treatment had no effect on aiding recovery from Day-1 to Day-2 as performance on Day-2 was not different between treatments. During the fatigue test, VO2 peaked at 60% of completion time for POMS and at 80% of completion time for PLA. The highest VO2 obtained during the fatigue trial corresponded to 99% of VO2max that was achieved during preliminary testing (Table 1.8).

*Thermoregulatory responses:* Tcore, Tskin, and Tbody were not different between trials. Tcore at the start of the fatigue trial was 37.7 $^{o}$C for both trials and increased to 38.3$^{o}$C. Tcore increased at a rate of approximately 0.1$^{o}$C/min. Tskin was maintained between 32.1$^{o}$C and 32.3$^{o}$C during the first 20% of the fatigue trial and then

decreased by 0.4$^{o}$C until the final portion of the trial. Tbody, like Tcore, increased throughout the course of the trial and was 0.5$^{o}$C higher at fatigue than start (Table 1.8).

*Cardiovascular responses:* There were no significant differences in HR, SV, or Q for the two treatments (Table 1.8). The HR response was nearly identical for both trials. Over the course of the fatigue trial HR increased to 181.2 and 181.5 bpm for PLA and POMS, respectively. No significant change in SV was observed during the fatigue trial. This finding is in agreement with Day-1 data and indicates that SV did not significantly increase beyond 74% of VO2max. CO peaked just prior to fatigue (i.e.; at the final time point) and was increased by 4 l/min at this time point when compared to the starting value (Table 1.8).

*NIRS and muscle oxygenation:* There was no effect of treatment on any of the NIRS variables measured (Table 8). However, significant changes over time did occur for OxSat and HHb. OxSat declined over the duration of the fatigue trial with final values at fatigue being 5% lower than starting values. HHb increased 8.5% (PLA) and 9.7% (POMS) over the course of the fatigue trial with most of the increase (~ 60%) in HHb occurring during the final 40% (i.e.; during the last 2.5 minutes) of the exercise bout. The time course with which VO2 and HHb increased during the fatigue trial is not similar as most of the increase in VO2 (~90%) occurred during the first 40% (i.e.; during the first 2.5 minutes) of the fatigue bout. This mismatch in VO2 and HHb may have implications for capillary blood flow and oxygen consumption during fatigue as described in Figure 1.4.

**Discussion:**

The purpose of this study was to determine if oral antioxidant supplementation can improve exercise performance in the heat and aid in recovery from exhaustive exercise. We hypothesized that antioxidant supplementation might improve exercise performance and that this improvement would be associated with alterations in cardiovascular and thermoregulatory function during exercise. The primary finding of this study is that antioxidant supplementation did not improve performance during prolonged exhaustive exercise (one hour exercise including 10 minute time trial) or during high intensity exercise (time to fatigue at VO2max) in the heat. Another novel finding afforded by the back to back days of high intensity exhaustive exercise showed that antioxidant supplementation did not aid in recovery from an exhaustive bout of exercise as there was no difference in performance from Day-1 to Day-2. Furthermore, variables associated with performance; gross cycling efficiency, blood lactate accumulation, maximal neuromuscular power, and rating of perceived exertion were not altered by POM supplementation. Accordingly, the cardiovascular and thermoregulatory responses were not different between the treatments.

This study is important as the use and popularity of antioxidant supplements has dramatically increased in recent years. Despite a rapid growth in popularity, scientific validation of the ergogenic benefits of antioxidants remains scarce. Antioxidants have been shown to improve (Medved *et al.*, 2004a; Medved *et al.*, 2004b; MacRae & Mefferd, 2006; McKenna *et al.*, 2006; McKenna *et al.*, 2008; McKenna & Hargreaves,

2008; Davis *et al.*, 2009), have no effect (Cheuvront *et al.*, 2009; Nieman *et al.*, 2009; Utter *et al.*, 2009), or decrease (Gomez-Cabrera *et al.*, 2008) exercise performance. Similarly, adaptations associated with exercise have been shown to be improved (Davis *et al.*, 2009), not changed (Gomez-Cabrera *et al.*, 2008), or decreased, with exercise (Lescaudron *et al.*, 1999; Richardson *et al.*, 2007; Gomez-Cabrera *et al.*, 2008; Wray *et al.*, 2009). The efficacy of antioxidant supplementation is complex and will undoubtedly be dependent on the population (healthy vs. diseased, young vs. old) (Kirby *et al.*, 2009) and the mode of exercise testing/training (endurance vs. resistance).

The rationale behind our focus on the cardiovascular and thermoregulatory function during exercise originated from the finding that POMS has been shown to increase NO bioavailability by protecting NO from oxidative destruction (Ignarro *et al.*, 2006). Given that NO has important roles in cutaneous blood flow (Kellogg *et al.*, 1998), thermoregulatory control of sweating during exercise (Welch *et al.*, 2009), and skeletal muscle blood flow (Boushel *et al.*, 2002; Mortensen *et al.*, 2007), we hypothesized that POMS would reduce the CV strain and improve thermoregulation during exercise in the heat. This was apparently not the case for our well trained subjects as there were no differences in CV or thermoregulatory function between the treatments.

During exercise there is an increase in reactive oxygen species (ROS) and free radical production (Davies *et al.*, 1982; Powers & Jackson, 2008). Originally the increase in ROS and free radicals were simply thought of as damaging or toxic agents of in vivo

biochemistry; however, free radicals are now becoming recognized as important molecules necessary for maintaining cellular homeostasis (Richardson *et al.*, 2007). Oxidative stress may play a necessary or regulatory role in many physiological processes and functions; mitochondrial biogenesis, vascular function, muscle regeneration, and inflammation. Based upon this theory, disrupting or reducing the normal increase in oxidative stress caused by exercise may reduce or attenuate the adaptations associated with exercise. That being said there are situations in which oxidative stress is chronic (e.g.; aging, disease) and normal function is diminished as a result of this chronic oxidative stress. This study was designed in order to increase the oxidative stress that is associated with exercise by performing high intensity exercise with the addition of a heat stress. Both high intensity exercise and heat stress have been shown to induce an elevation in oxidative stress beyond normal conditions (McAnulty *et al.*, 2005; Tyldum *et al.*, 2009). In order to test the efficacy of the antioxidant supplement it is important to create a situation in which the oxidative stress was elevated.

The antioxidants found in the POMS supplement contain high concentrations of polyphenols, specifically elligatannis, which have been shown to possess higher antioxidant potency when compared to other polyphenol rich fruits (Seeram *et al.*, 2008a; Seeram *et al.*, 2008b). Pharmacokinetic analysis revealed that plasma levels of ellagic acid, a metabolite of the POMS supplement, peaked 1 and 2 hours post consumption and was present in some urine samples 48 hours after initial ingestion (Seeram *et al.*, 2006). Recent work from our lab (Trombold *et al.*, in press)

demonstrated that POM supplementation (identical composition as that used in the current study) was successful at attenuating the muscle weakness and soreness experience following eccentric exercise. Given that subjects consumed the supplement twice daily for 7 days and consumed the supplement approximately 30 minutes before exercise we are confident that the active antioxidants from the supplement were in the system during exercise. Furthermore, similar polyphenol antioxidants (POM specifically) have been shown to have high biological activity and potent treatment effects in clinical conditions associated with oxidative stress and/or vascular dysfunction such as type 2 diabetes (Rosenblat *et al.*, 2006), atherosclerosis (Aviram *et al.*, 2004), cancer (Adams *et al.*, 2006), and rheumatoid arthritis (Shukla *et al.*, 2008).

While the antioxidant supplementation used in the current study did not have any effect on performance, cardiovascular, and thermoregulatory function, there is evidence supporting the role of such supplementation during conditions of disease or dysfunction. The present study used highly trained endurance athletes which may have an up-regulated endogenous antioxidant enzyme system capable of coping with the increase in oxidative stress brought about by high intensity exercise in the heat. Trombold et al. (Trombold *et al.*, in press) showed that following damaging eccentric exercise both novice and experienced resistance trained individuals exhibited an accelerated rate of muscle strength recovery at 48 and 72 hours post exercise. A recent study (Nieman *et al.*, 2009) showed that quercetin (flavanoid antioxidant) supplementation was effective at reducing inflammation associated with continuous

days of prolonged cycling exercise but did not affect mitochondrial biogenesis. Chronic supplementation with polyphenols has been shown to improve endothelial nitric oxide synthase (eNOS) and vasoreactivity in response to shear stress in patients with cardiovascular disease (de Nigris *et al.*, 2007). A possible mechanism for the increased vascular function may be due to an increase in NO bioavailability as POMS has been shown to augment the biological action of NO by protecting the molecule from oxidative destruction (Ignarro *et al.*, 2006). Ignarro et al. (Ignarro *et al.*, 2006) showed that POMS was only effective at upregulating eNOS expression and endothelial function in dysfunctional endothelial cells and not in healthy endothelial cells. This might be a possible reason why we showed no difference in CV and thermoregulatory function in our healthy, well trained subjects. Other studies (Plotnick *et al.*, 2003; Barringer *et al.*, 2008) created an acute state of metabolic dysfunction in humans via consumption of a high fat meal and showed that polyphenol supplementation was effective at preventing vascular dysfunction following the meal. Similarly, mice fed a high fat diet in combination with resveratrol showed improved insulin sensitivity and reduced mortality despite increased bodyweight (Baur *et al.*, 2006). Additionally, the resveratrol fed mice displayed reduced hepatic pathology, preserved mitochondria content, and improved motor coordination over their lifespan when compared to control mice on the high fat diet. These findings along with the present study provide support for the idea that antioxidant supplement may be of most benefit in the presence of disease

(cardiovascular, metabolic), disuse (inactivity, sedentary lifestyle), and dysfunction (inflammation, metabolic).

Despite the previously described argument against the ergogenic benefits of antioxidant supplements, there are a few studies that have shown dramatic improvements in exercise performance following administration of antioxidants. However, we are aware of only one study that showed improved exercise performance with *oral* antioxidant supplementation in healthy individuals (MacRae & Mefferd, 2006). This was the impetus for performing the current study. Collectively, investigations into the effectiveness of supplementation with antioxidant vitamins E and C show that these vitamins do not improve human exercise performance (Clarkson, 1995; Kanter & Williams, 1995; Powers *et al.*, 2004). However, rather compelling evidence has been gathered showing the ergogenic effect of the free radical scavenger, N-acetylcysteine (NAC) (Travaline *et al.*, 1997; Medved *et al.*, 2004a; Medved *et al.*, 2004b; Matuszczak *et al.*, 2005; McKenna *et al.*, 2006; McKenna *et al.*, 2008; McKenna & Hargreaves, 2008). Pertinent to the present study, a series of studies (Medved *et al.*, 2004a; Medved *et al.*, 2004b; McKenna *et al.*, 2006; McKenna & Hargreaves, 2008; Murphy *et al.*, 2008) was performed investigating the effects of NAC infusion on time to fatigue and the mechanisms responsible for the observed improvements in performance. Medved et al. (Medved *et al.*, 2004b) infused NAC prior to and during prolonged cycle exercise and showed a 26% improvement in performance (time to fatigue at 92% of VO2max). The increase in performance was attributed to enhanced muscle cysteine and glutathione

availability. A follow-up study (Medved *et al.*, 2004a) revealed that the improvement in time to fatigue was correlated with VO2max, indicating that the most fit individuals are most likely to benefit from the NAC supplementation and that the improvement was also associated with improved K+ regulation. McKenna et al. (McKenna *et al.*, 2006) showed that NAC attenuates muscle fatigue during cycling exercise by preserving Na+/K+ pump activity leading to the improved K+ regulation. Discrepancies between the aforementioned studies and the present study may be due to a multitude of factors; 1) method of administration (intravenous infusion vs. oral consumption), 2) the amount of antioxidant administered (physiological vs. supraphysiological), 3) the type of antioxidant provided (NAC vs. polyphenol), and 4) the environmental conditions under which exercise was performed (warm vs. moderate). While all four of these differences may contribute to the discrepancies, the most likely are the manner in which and the amount of the antioxidant that was administered. The use of an intravenous infusion of NAC prior to and during the exercise bout allowed for the delivery of a supraphysiological dose of the antioxidant. While the NAC infusion studies provided valuable information regarding mechanisms related to muscle fatigue and the role of ROS and free radicals on muscle fatigue, they do not, from a practical and application oriented viewpoint, provide information regarding the ergogenic benefit of oral antioxidant supplementation.

Oral supplementation with physiological dosages of the antioxidant quercetin has shown equivocal results regarding exercise performance. MacRae et al. (MacRae &

Mefferd, 2006) found a small but significant 3% increase in 30 kilometer time trial performance after 6 weeks of quercetin supplementation. Davis et al. (Davis *et al.*, 2009) fed mice quercetin for 7 days and showed improved exercise tolerance (time to fatigue on a treadmill) and mitochondrial biogenesis. However, in support of the findings of the current study, Cheuvront et al. (Cheuvront *et al.*, 2009) reported that quercetin supplementation (2,000 mg) did not affect total work performed during a 15 minute time trial in the heat (40 C; 20 to 30% RH) or alter the pacing strategy during the time trial. In agreement with the current study, quercetin did not have any impact on physiological or perceptual measures during exercise. Neiman et al. (Nieman *et al.*, 2009) found no difference between quercetin and placebo in any performance related measurement. These previous findings, coupled with the results of the present study, indicate that antioxidant supplementation, in general, does not improve exercise performance in healthy individuals.

Exercise performance in the present study was maintained during POMS supplementation. However, recent findings argue that acute and chronic antioxidant supplementation in healthy individuals may disrupt or have a negative impact on physiological function and may attenuate or reduce the positive outcomes associated with exercise training. Richardson et al. (Richardson *et al.*, 2007) reduced free radical production in healthy subjects via an oral antioxidant cocktail. This reduction in free radicals disrupted the balance between pro and antioxidant forces and negatively impaired vascular function by reducing blood flow. Exercise training reduced blood

pressure in slightly hypertensive elderly men yet when exercise was combined with antioxidant administration the beneficial improvements yielded from the exercise training was blunted (Wray *et al.*, 2009). Recent findings (Gomez-Cabrera *et al.*, 2008) on rats showed that vitamin C administration attenuated adaptations to exercise training. Endurance trained rats improved exercise time to exhaustion nearly 3 fold (99 to 284 min; 187% increase) whereas the group that also consumed vitamin C exhibited a marked reduction in improvement of endurance capacity (101 to 128 min; 26% increase). Adaptations associated with resistance exercise training may also be negatively influenced as the normal inflammatory response to muscle damage appears to have a stimulatory effect on skeletal muscle adaptations, specifically muscle hypertrophy (Lescaudron *et al.*, 1999). In the present study, the 7 day period of supplementation may have been short enough to not negatively impact exercise performance. Although not directly measured in the current study there is no indication that skin blood flow was negatively affected as skin temperature, sweat rate, and the cardiovascular and thermoregulatory responses were not altered by the treatment. Exercise in healthy individuals produces acute increases in oxidative stress that ultimately leads to an up-regulation of the body's natural defense mechanisms against ROS and free radicals making supplementation with antioxidant unnecessary. Antioxidant supplementation may be warranted in situations in which oxidative stress is chronically elevated (disease and dysfunction). Under these conditions exogenous

antioxidants appear to compensate for the inability of the endogenous antioxidant systems to combat the persistent increase in oxidative stress.

Another novel and important finding of the present study is the manner in which HHb changed over the course of the fatigue trial. During the fatigue trial the majority of the increase in oxygen consumption occurred during the first 40% of the exercise bout and was maintained until 60% of completion time until fatigue (Figure 1.5). Breath by breath measurements of VO2 were not made therefore exact calculation of the oxygen uptake kinetics cannot be made. HHb, which can be used to estimate muscle O2 extraction (Barstow & Mole, 1991; Grassi *et al.*, 1996; DeLorey *et al.*, 2003; Ferreira *et al.*, 2005; Harper *et al.*, 2006; Ferreira *et al.*, 2007; Boone *et al.*, 2009; Krustrup *et al.*, 2009), increased slightly during the first 60% of the exercise bout but did not increase significantly until just prior to fatigue. Whole body VO2 can be integrated with HHb to give an estimation of capillary blood flow (Qcap) to the active muscle tissue (Ferreira *et al.*, 2005; Harper *et al.*, 2006; Ferreira *et al.*, 2007; Boone *et al.*, 2009). Estimated Qcap plateaued after 40% of the exercise bout is completed and is reduced just prior to fatigue (Figure 1.5). Studies examining leg blood flow during similar fatiguing exercise bouts have shown that leg blood flow plateaus at approximately 50% of completion time (Gonzalez-Alonso & Calbet, 2003; Gonzalez-Alonso *et al.*, 2004; Mortensen *et al.*, 2005). A reduction in leg blood flow has not been previously reported, however, the techniques previously used measured flow across a whole limb. Therefore, flow to tissues other than the active muscle may have contributed to the overall blood flow

measurement (Harper *et al.*, 2006). It is conceivable that blood flow does not increase to the same extent to the different muscle groups of the leg (glutes, quadriceps, hamstrings) during upright cycling. The current finding that Qcap of the vastus lateralis is reduced during fatigue should be interpreted with caution as the NIRS measurements were made on only 5 subjects. Despite the low subject number, such a reduction in capillary blood flow may provide insight into peripheral muscle fatigue during high intensity exercise.

Based on the findings of this study exercise performance in the heat was not improved by POMS supplementation. Accordingly, POMS had no effect on the cardiovascular or thermoregulatory response to exercise or any variable related to performance (oxygen consumption, gross efficiency, and rating of perceived exertion). There is a growing body of literature indicating that antioxidant supplementation in healthy individuals may result in negative outcomes by altering the balance between pro and antioxidant regulation of many physiological processes.

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Figure 1.1A: Experimental timeline for familiarization session 2 and experimental testing Day - 1

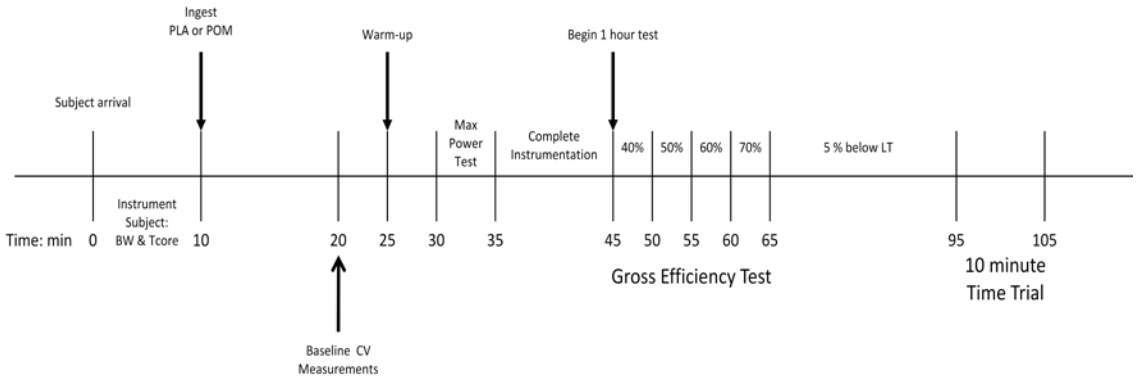
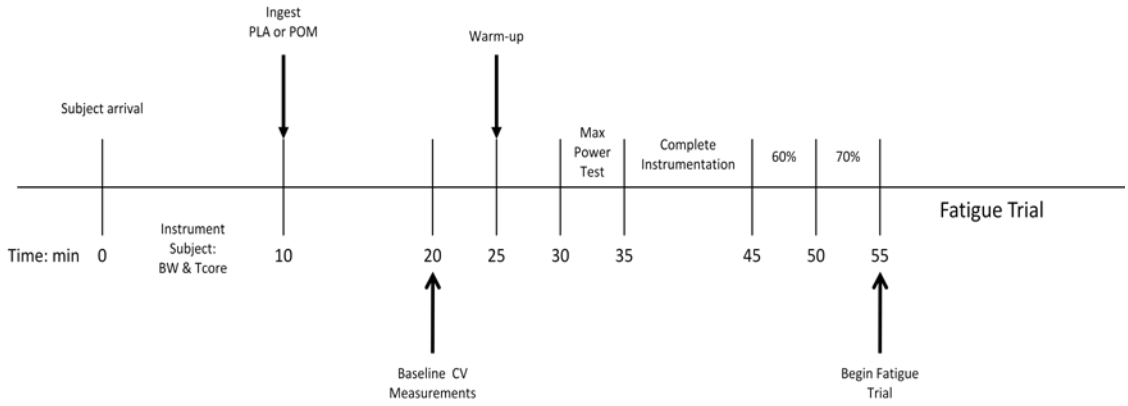



Figure 1.1B: Experimental timeline for familiarization session 3 and experimental testing Day - 2



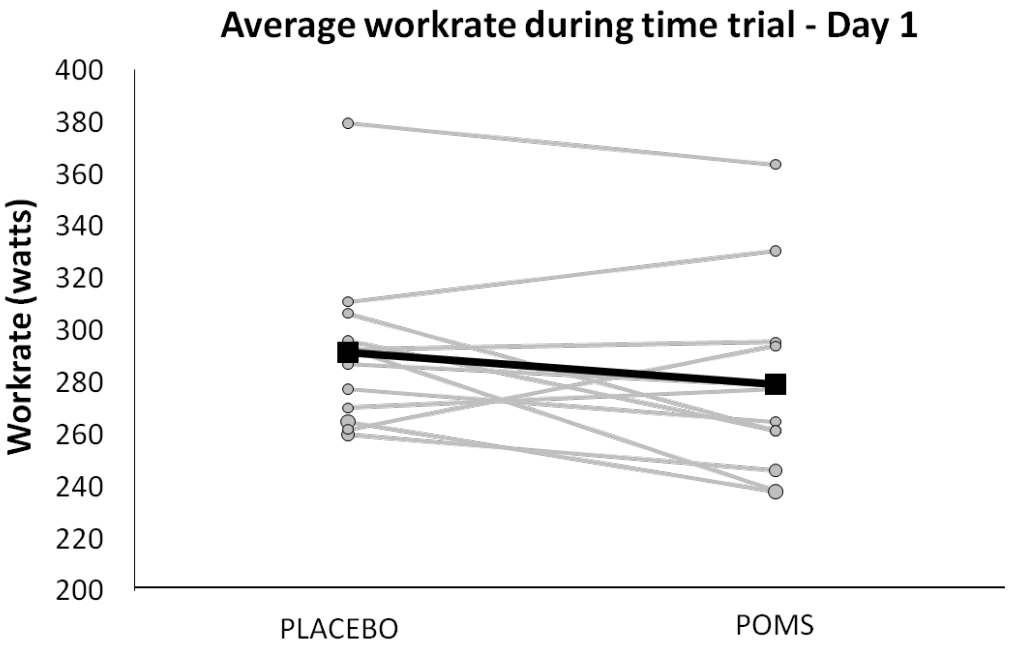



Figure 1.2: Average workrate during the 10 minute time trial performed on Day-1 for both PLA and POMS. Individual data of the 12 subjects and the mean response, represented by solid black line, is presented. There was no difference in average workrate between PLA and POMS.

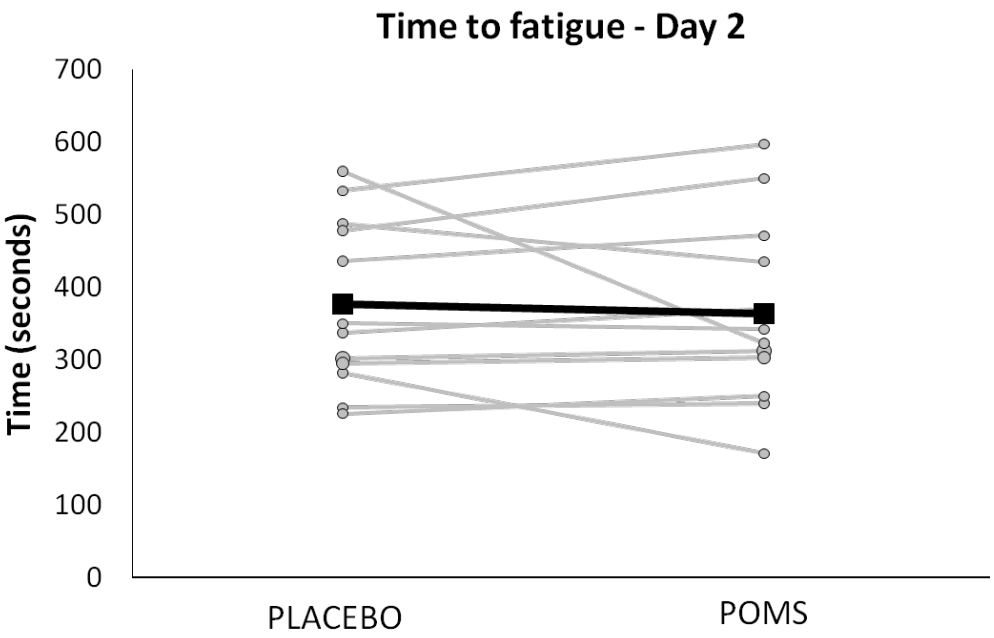



Figure 1.3: Time to fatigue during the constant load performance test performed on Day-2 for both PLA and POMS. Individual data of the 12 subjects and the mean response, represented by solid black line, is presented. There was no difference in time to fatigue between PLA and POMS.

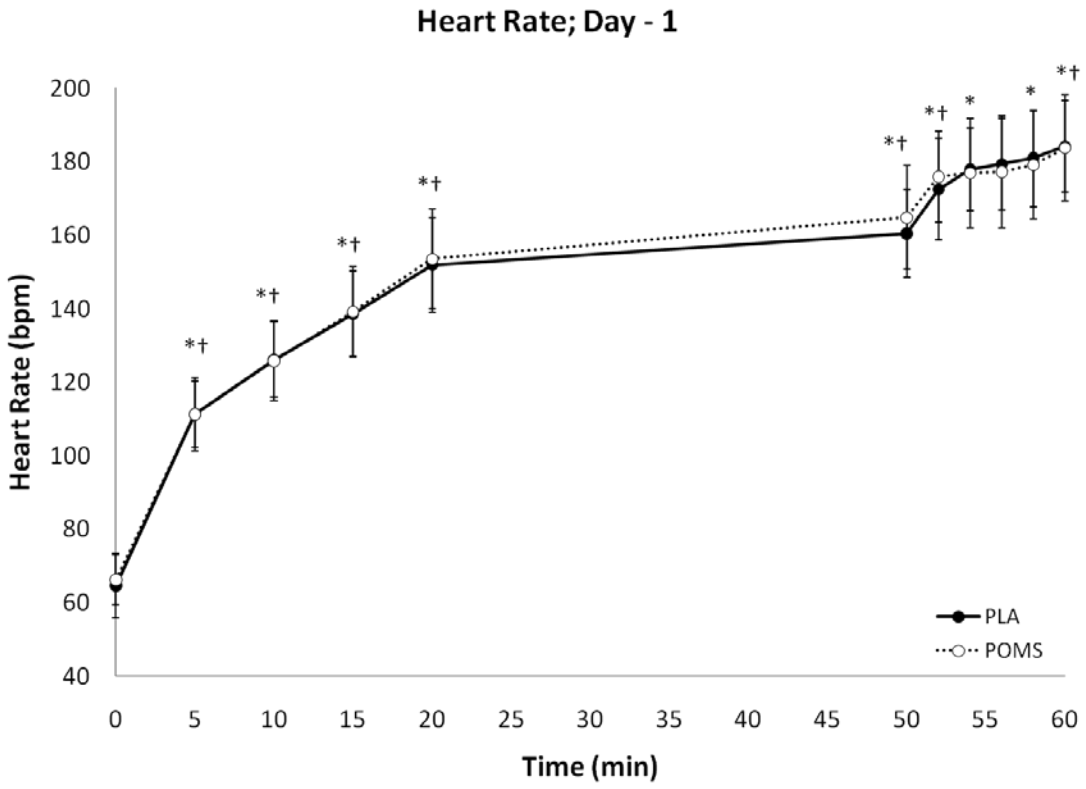



Figure 1.4: Values are mean ± SE for 12 subjects. Heart rate response for POMS and PLA during one hour exercise bout on Day - 1. * Indicates significant difference from previous value for PLA and † indicates significant difference from previous value for POMS, $p < 0.05$.

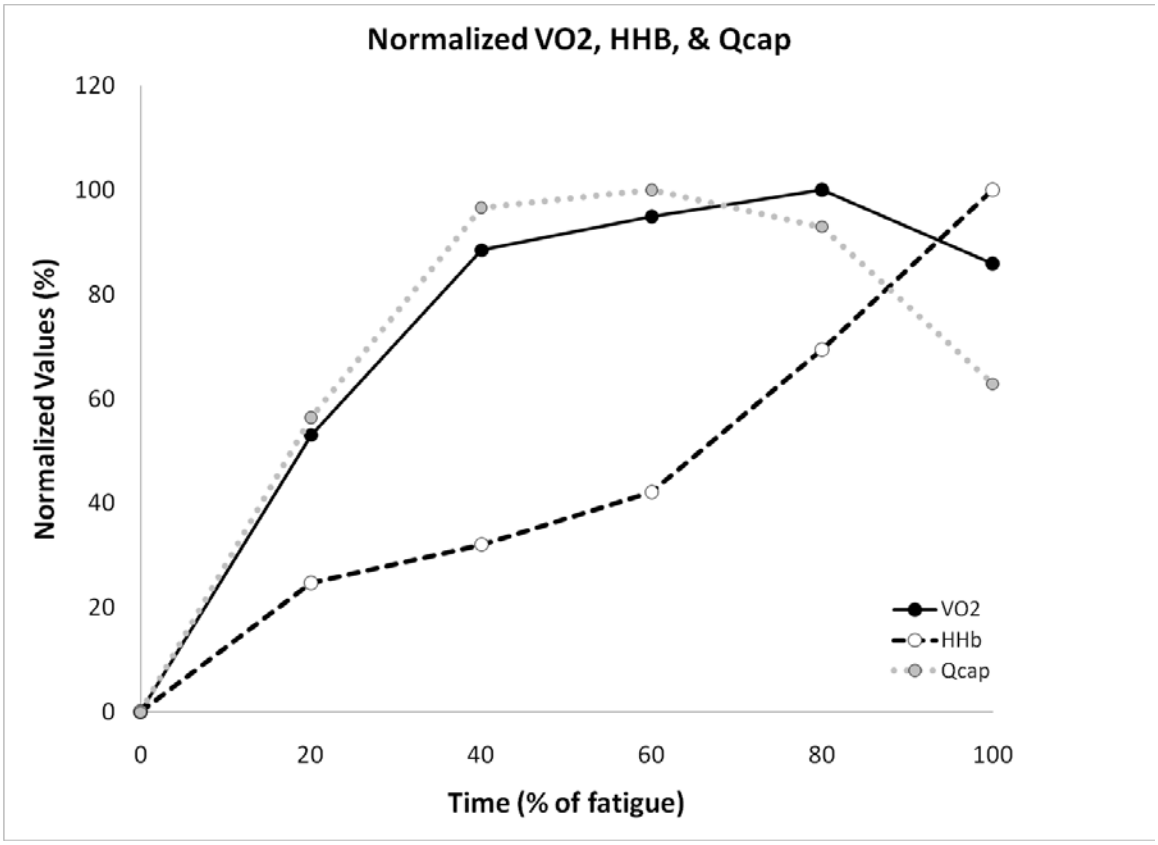



Figure 1.5: Mean responses for normalized oxygen consumption (% VO2), deoxygenated hemoglobin (% HHb), and estimated capillary blood flow (%Qcap). Data was normalized based on the following equation range; % normalized value = [( value of interest - min) / (max - min)] (Belardinelli *et al.*, 1995).

Table 1.1: *Change in Bodyweight; Day - 1*

| | Placebo | POMS |
|---|---|---|
| Pre Bodyweight, kg | 74.2 ± 9.1 | 74.4 ± 9.1 |
| Post Bodyweight, kg | 73.7 ± 8.8* | 73.9 ± 9.1* |

Values are mean ± SD of 12 subjects. * Indicates significant decrease from pre bodyweight, $p < 0.05$.

Table 1.2: *Exercise intensity,respiratory responses, and gross cycling efficiency; Day - 1*

| TIME, min | | 5 | 10 | 15 | 20 | 20 to 50 |
|---|---|---|---|---|---|---|
| Workrate, watts | | | | | | |
| | PLA | 99 ± 11 | 144 ± 12* | 189 ± 15* | 234 ± 19* | 229 ± 17 |
| | POM | 99 ± 11 | 144 ± 12* | 189 ± 15* | 234 ± 19* | 229 ± 17 |
| VO2, ml/min | | | | | | |
| | PLA | 1807 ± 147 | 2347 ± 240* | 2760 ± 218* | 3271 ± 224* | |
| | POM | 1882 ± 171 | 2354 ± 192* | 2839 ± 235* | 3324 ± 284* | |
| % VO2max | | | | | | |
| | PLA | 40.6 ± 3.7 | 52.6 ± 3.7* | 62.0 ± 3.8* | 73.5 ± 4.4* | |
| | POM | 42.4 ± 4.3 | 52.9 ± 4.2* | 63.8 ± 4.6* | 74.6 ± 5.1* | |
| VCO2, l/min | | | | | | |
| | PLA | 1517 ± 92 | 2031 ± 188* | 2398 ± 162* | 2886 ± 159* | |
| | POM | 1580 ± 143 | 2023 ± 144* | 2465 ± 190* | 2940 ± 245* | |
| RER | | | | | | |
| | PLA | 0.84 ± 0.03 | 0.87 ± 0.03* | 0.87 ± 0.03 | 0.88 ± 0.04* | |
| | POM | 0.84 ± 0.03 | 0.86 ± 0.03* | 0.87 ± 0.03* | 0.89 ± 0.04* | |
| GE, % | | | | | | |
| | PLA | 16.2 ± 1.5 | 18.1 ± 1.4* | 20.1 ± 1.0* | 20.9 ± 1.2* | |
| | POM | 15.6 ± 1.5 | 18.1 ± 1.3* | 19.6 ± 1.1* | 20.6 ± 0.9* | |

Values are mean ± SD of 12 subjects. Oxygen consumption (VO2), relative oxygen consumption (%VO2max), CO2 consumption (VCO2), respiratory exchange ratio (RER), gross efficiency (GE). * Indicates significant difference from previous value, $p < 0.05$.

Table 1.3: *Performance during time trial; Day - 1*

| Time | PLA (watts) | POMS (watts) |
|---|---|---|
| 0 to 2.5 min | 310.6 ± 32.0 | 307.5 ± 30.3 |
| 2.5 to 5 min | 290.5 ± 41.6* | 271.8 ± 44.9* |
| 5 to 7.5 min | 277.6 ± 36.6* | 259.5 ± 44.6* |
| 7.5 to 10 min | 288.2 ± 29.3 | 278.2 ± 40.3* |

Values are mean ± SD of 12 subjects. Performance was divided into 2.5 min quartiles to determine if treatment had any effect on pacing strategy during the 10 min time trial. * Indicates significant difference from previous value, $p < 0.05$.

Table 1.4: *Blood lactate and rating of percieved exertion; Day - 1*

| Time, min | 5 | 30 | 45 | post TT |
|---|---|---|---|---|
| Lactate | | | | |
| PLA | 1.3 ± 0.3 | 2.6 ± 0.9* | | 8.2 ± 2.4* |
| POM | 1.4 ± 0.4 | 2.7 ± 0.9* | | 8.1 ± 3.3* |
| RPE | | | | |
| PLA | | 13.3 ± 1.2 | 13.5 ± 1.3 | |
| POM | | 13.3 ± 0.9 | 14.1 ± 1.3 | |

Values are mean ± SD of 12 subjects. Post TT lactate was obtained 3 min after completion of the TT. * Indicates significant difference from previous value, $p < 0.05$.

Table 1.5: *Maximal Neuromuscular Power*

| | Placebo (Day-1) | POMS (Day-1) | Placebo (Day-2) | POMS (Day -2) |
|---|---|---|---|---|
| Pmax, watts | 1250 ± 231 | 1240 ± 229 | 1240 ± 214 | 1243 ± 258 |
| IP, watts | 2027 ± 384 | 2029 ± 362 | 2027 ± 336 | 2046 ± 415 |
| RPM | 120.9 ± 8.7 | 120.7 ± 8.6 | 119.6 ± 9.1 | 116.7 ± 8.1 |
| Pmax, w/kg | 16.8 ± 1.8 | 16.6 ± 1.9 | 16.7 ± 1.6 | 16.6 ± 2.0 |

Values are mean ± SD of 12 subjects. Maximal neuromuscular power (Pmax), instanteous maximal power (IP), revolutions per minute at maximal power (RPM), and maximal power per kilogram bodyweight (Pmax, W/kg). No significant differences between treatments or over time were observed.

Table 1.6: *Thermoregulatory and Cardiovascular reponses; Day - 1*

| TIME, min | rest | 5 | 10 | 15 | 20 | 50 | 52 | 54 | 56 | 58 | 60 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Tcore , ºC | | | | | | | | | | | |
| PLA | 37.30 ± 0.30 | 37.37 ± 0.32* | 37.50 ± 0.27* | 37.65 ± 0.25* | 37.84 ± 0.25* | 38.48 ± 0.28* | 38.52 ± 0.29* | 38.61 ± 0.30* | 38.71 ± 0.31* | 38.81 ± 0.32* | 38.90 ± 0.34* |
| POM | 37.27 ± 0.22 | 37.31 ± 0.21 | 37.44 ± 0.20* | 37.60 ± 0.21* | 37.79 ± 0.23* | 38.53 ± 0.27* | 38.58 ± 0.29* | 38.65 ± 0.29* | 38.73 ± 0.29* | 38.80 ± 0.28* | 38.87 ± 0.28* |
| Tskin , ºC | | | | | | | | | | | |
| PLA | 32.00 ± 0.91 | 32.22 ± 0.49 | 32.25 ± 0.45 | 32.31 ± 0.49 | 32.14 ± 0.67 | 31.03 ± 0.76* | 31.14 ± 0.79 | 31.08 ± 0.68 | 30.89 ± 0.71 | 31.02 ± 0.75 | 31.05 ± 0.96 |
| POM | 32.56 ± 0.71† | 32.37 ± 0.63 | 32.21 ± 0.52 | 32.03 ± 0.40 | 32.05 ± 0.39 | 31.25 ± 1.04* | 31.07 ± 1.07 | 30.98 ± 1.05 | 30.94 ± 0.91 | 30.76 ± 1.00 | 30.58 ± 1.21 |
| Tbody , ºC | | | | | | | | | | | |
| PLA | 36.61 ± 0.25 | 36.70 ± 0.32* | 36.82 ± 0.28* | 36.96 ± 0.24* | 37.10 ± 0.25* | 37.51 ± 0.29* | 37.56 ± 0.28* | 37.63 ± 0.27* | 37.70 ± 0.28* | 37.79 ± 0.31* | 37.88 ± 0.35* |
| POM | 36.65 ± 0.22 | 36.67 ± 0.22 | 36.76 ± 0.21* | 36.88 ± 0.21* | 37.04 ± 0.22* | 37.59 ± .28* | 37.60 ± 0.29 | 37.65 ± 0.28* | 37.72 ± 0.29* | 37.75 ± 0.28 | 37.80 ± 0.31 |
| HR, bpm | | | | | | | | | | | |
| PLA | 64.6 ± 8.9 | 111.2 ± 9.1* | 126.1 ± 10.2* | 138.6 ± 11.7* | 152.0 ± 12.8* | 160.5 ± 11.9* | 172.5 ± 13.7* | 177.9 ± 11.3* | 179.3 ± 12.4 | 180.9 ± 13.1* | 184.2 ± 12.5* |
| POM | 66.2 ± 6.8 | 111.2 ± 9.9* | 125.8 ± 10.8* | 139.2 ± 12.1* | 153.5 ± 13.6* | 164.8 ± 14.1* | 175.9 ± 12.3* | 177.0 ± 14.9 | 177.2 ± 15.3 | 179.2 ± 14.6 | 183.7 ± 14.4* |
| SV, ml/beat | | | | | | | | | | | |
| PLA | 88.4 ± 11.1 | 115.6 ± 12.8* | 118.3 ± 12.9* | 121.4 ± 13.4* | 122.8 ± 13.9 | 123.0 ± 14.3 | 124.8 ± 15.3 | 127.4 ± 17.6 | 128.6 ± 19.0 | 130.1 ± 21.7 | 127.6 ± 15.0 |
| POM | 88.8 ± 12.1 | 115.6 ± 16.8* | 118.4 ± 16.6* | 121.5 ± 16.4* | 124.2 ± 17.1* | 125.1 ± 17.2 | 125.2 ± 17.5 | 127.6 ± 17.7 | 125.9 ± 18.1 | 127.6 ± 17.2 | 128.6 ± 19.2 |
| CO, l/min | | | | | | | | | | | |
| PLA | 5.8 ± 1.1 | 12.8 ± 1.7* | 14.9 ± 1.8* | 16.8 ± 2.1* | 18.6 ± 2.2* | 19.7 ± 2.0* | 21.4 ± 2.5* | 22.6 ± 2.7* | 23.0 ± 3.3 | 23.5 ± 3.8 | 23.4 ± 2.6 |
| POM | 5.9 ± 0.8 | 12.8 ± 1.8* | 14.8 ± 2.0* | 16.8 ± 2.0* | 19.0 ± 2.5* | 20.5 ± 2.5* | 22.0 ± 3.0* | 22.6 ± 3.5 | 22.3 ± 3.8 | 22.9 ± 3.8 | 23.6 ± 4.1 |
| SBP, mmHg | | | | | | | | | | | |
| PLA | 122.4 ± 5.7 | 158.4 ± 17.5* | 173.8 ± 15.7* | 181.7 ± 15.9* | 193.1 ± 16.* | 191.7 ± 15.1 | 205.5 ± 14.4* | 211.3 ± 20.2 | 203.8 ± 18.1 | 211.5 ± 22.5* | 205.8 ± 16.6 |
| POM | 125.7 ± 5.4 | 157.4 ± 16.8* | 175.8 ± 14.9* | 181.8 ± 17.3 | 197.1 ± 14.7* | 191.6 ± 20.0 | 196.7 ± 15.0 | 200.8 ± 12.2 | 200.8 ± 13.7 | 199.1 ± 20.3 | 203.1 ± 20.0 |
| DBP, mmHg | | | | | | | | | | | |
| PLA | 83.0 ± 6.5 | 82.3 ± 13.4 | 78.4 ± 11.4 | 73.4 ± 12.4* | 71.3 ± 12.5 | 74.6 ± 10.5 | 77.1 ± 10.2 | 79.8 ± 10.9 | 73.9 ± 11.6 | 76.9 ± 14.0 | 71.8 ± 13.6 |
| POM | 84.8 ± 8.6 | 80.3 ± 12.0 | 76.4 ± 12.1 | 73.8 ± 10.0 | 70.9 ± 11.1 | 77.9 ± 14.9 | 72.7 ± 13.4 | 76.4 ± 13.8 | 78.5 ± 11.7 | 74.2 ± 11.6 | 78.4 ± 11.0 |
| MAP, mmHg | | | | | | | | | | | |
| PLA | 96.1 ± 4.9 | 107.6 ± 10.8 | 110.2 ± 10.3 | 109.5 ± 10.7 | 111.9 ± 9.7* | 113.7 ± 8.2 | 119.9 ± 6.6 | 123.7 ± 9.3 | 117.2 ± 9.7 | 121.8 ± 10.8 | 116.5 ± 10.1 |
| POM | 98.4 ± 6.4 | 106.0 ± 11.0 | 109.6 ± 11.0 | 109.8 ± 10.1 | 113.0 ± 8.6 | 115.8 ± 11.7 | 114.0 ± 9.6 | 117.9 ± 10.9 | 119.3 ± 9.7 | 115.8 ± 12.1 | 119.9 ± 11.2 |
| TPR, pru | | | | | | | | | | | |
| PLA | 17.30 ± 3.54 | 8.56 ± 1.64* | 7.54 ± 1.35* | 6.65 ± 1.20* | 6.13 ± 1.11* | 5.83 ± 0.71 | 5.68 ± 0.87 | 5.56 ± 0.86 | 5.19 ± 0.91 | 5.29 ± 0.82 | 5.04 ± 0.86* |
| POM | 17.12 ± 2.79 | 8.46 ± 1.75* | 7.58 ± 1.71* | 6.64 ± 1.21* | 6.08 ± 1.17* | 5.77 ± 1.19 | 5.30 ± 1.02* | 5.39 ± 1.31 | 5.52 ± 1.24 | 5.20 ± 1.16 | 5.22 ± 1.04 |

Values are mean ± SD of 12 subjects. Core temperature (Tcore), mean skin temperature (Tskin), body temperature (Tbody), heart rate (HR), stroke volume (SV), cardiac output (Q), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), and total peripheral resistance (TPR). * Indicates significant difference from previous value,† indicates significant difference between PLA and POMS, $p < 0.05$.

Table 1.7: *Near Infrared Spectroscopy meausres during exercise; Day - 1*

| TIME, min | 5 | 10 | 15 | 20 | 50 | 52 | 54 | 56 | 58 | 60 |
|---|---|---|---|---|---|---|---|---|---|---|
| OxSat, % | | | | | | | | | | |
| PLA | 60.9 ± 4.1 | 59.6 ± 4.3* | 56.1 ± 4.7* | 53.9 ± 4.4 | 54.9 ± 3.4 | 52.6 ± 4.3* | 51.8 ± 5.4 | 51.6 ± 5.6 | 51.6 ± 5.6 | 52.0 ± 5.7 |
| POM | 61.7 ± 5.4 | 60.8 ± 8.0 | 58.2 ± 7.7* | 57.0 ± 5.9 | 55.1 ± 4.8* | 54.2 ± 4.8 | 53.5 ± 4.7 | 52.5 ± 3.8 | 52.2 ± 3.0 | 52.2 ± 3.1 |
| THC, um | | | | | | | | | | |
| PLA | 62.1 ± 5.2 | 64.1 ± 6.8 | 63.8 ± 7.9 | 64.2 ± 8.4 | 66.8 ± 8.5 | 67.2 ± 8.0 | 66.4 ± 8.7 | 66.5 ± 8.9 | 66.8 ± 8.8 | 67.1 ± 9.2 |
| POM | 63.7 ± 4.8 | 67.2 ± 6.1 | 67.9 ± 6.3 | 67.7 ± 5.5 | 67.1 ± 5.8 | 67.0 ± 7.0 | 66.9 ± 7.1 | 67.2 ± 6.2 | 67.4 ± 6.2 | 67.6 ± 6.2 |
| HbO, um | | | | | | | | | | |
| PLA | 37.9 ± 5.0 | 38.3 ± 5.9 | 36.0 ± 7.0 | 34.8 ± 6.8 | 36.7 ± 5.7 | 35.5 ± 6.0* | 34.5 ± 7.1 | 34.4 ± 7.2 | 34.6 ± 6.8 | 35.0 ± 7.2 |
| POM | 39.4 ± 5.0 | 41.0 ± 8.1 | 39.7 ± 8.1 | 38.6 ± 5.3 | 36.9 ± 3.7 | 36.2 ± 4.3 | 35.7 ± 4.4 | 35.2 ± 3.1 | 35.1 ± 2.4 | 35.1 ± 1.4 |
| HHb, um | | | | | | | | | | |
| PLA | 24.2 ± 2.5 | 25.8 ± 2.9* | 27.8 ± 2.4* | 29.4 ± 3.1 | 30.1 ± 4.1 | 31.7 ± 3.9* | 31.8 ± 4.2 | 32.0 ± 4.5 | 32.2 ± 4.9 | 32.1 ± 4.9 |
| POM | 24.3 ± 3.5 | 26.2 ± 5.0 | 28.2 ± 4.6* | 29.1 ± 4.7 | 30.2 ± 4.7 | 30.7 ± 5.1 | 31.1 ± 5.0 | 32.0 ± 4.7 | 32.3 ± 4.5 | 32.5 ± 5.0 |

Values are mean ± SD of 5 subjects. Oxygen saturation (OxSat), total hemoglobin content (THC), oxygenated hemoglobin (HbO), and deoxygenated hemoglobin (HHb). * Indicates significant difference from previous value, $p < 0.05$.

Table 1.8: *Respiratory, cardiovascular, thermoregulatory, and NIRS responses; Day - 2*

| TIME (% of completion) | | 0% | 20% | 40% | 60% | 80% | 100% |
|---|---|---|---|---|---|---|---|
| VO2, l/min | | | | | | | |
| | PLA | 3383 ± 287 | 3877 ± 414* | 4233 ± 316* | 4248 ± 295 | 4399 ± 336* | 4232 ± 459 |
| | POM | 3426 ± 412 | 3957 ± 433* | 4286 ± 409* | 4396 ± 430* | 4343 ± 383 | 4239 ± 347 |
| HR, bpm | | | | | | | |
| | PLA | 154.5 ± 14.5 | 165.7 ± 13.2* | 172.6 ± 12.5* | 176.3 ± 12.9* | 179.4 ± 12.3* | 181.2 ± 12.2* |
| | POM | 155.9 ± 14.3 | 165.9 ± 13.9* | 172.8 ± 13.3* | 176.5 ± 12.7* | 179.0 ± 12.3* | 181.5 ± 12.6 |
| SV, ml/beat | | | | | | | |
| | PLA | 127.3 ± 13.4 | 129.4 ± 13.5 | 130.4 ± 15.8 | 130.2 ± 14.6 | 129.6 ± 15.2 | 130.5 ± 16.0 |
| | POM | 129.6 ± 13.0 | 132.2 ± 17.1 | 132.9 ± 17.1 | 133.0 ± 14.9 | 132.9 ± 14.8 | 132.7 ± 16.7 |
| CO, l/min | | | | | | | |
| | PLA | 19.6 ± 1.9 | 21.4 ± 2.0* | 22.4 ± 2.4* | 22.9 ± 2.2 | 23.2 ± 2.6 | 23.5 ± 2.9 |
| | POM | 20.1 ± 1.9 | 21.8 ± 2.7* | 22.9 ± 2.7* | 23.4 ± 2.6* | 23.7 ± 2.6 | 24.0 ± 3.1 |
| Tcore, $^{o}$ C | | | | | | | |
| | PLA | 37.69 ± 0.19 | 37.74 ± 0.18* | 37.84 ± 0.18* | 37.97 ± 0.20* | 38.10 ± 0.26* | 38.25 ± 0.32* |
| | POM | 37.71 ± 0.22 | 37.77 ± 0.22 | 37.88 ± 0.24* | 38.01 ± 0.28* | 38.16 ± 0.34* | 38.31 ± 0.39* |
| Tskin, $^{o}$ C | | | | | | | |
| | PLA | 32.27 ± 0.36 | 32.30 ± 0.37 | 32.09 ± 0.41* | 31.93 ± 0.42* | 31.89 ± 0.52 | 31.95 ± 0.43 |
| | POM | 32.07 ± 0.66 | 32.15 ± 0.68 | 31.94 ± 0.68 | 31.87 ± 0.65 | 31.86 ± 0.67 | 31.74 ± 0.73 |
| Tbody, $^{o}$ C | | | | | | | |
| | PLA | 36.98 ± 0.18 | 37.04 ± 0.17* | 37.09 ± 0.16* | 37.18 ± 0.17* | 37.30 ± 0.21* | 37.43 ± 0.27* |
| | POM | 36.97 ± 0.22 | 37.04 ± 0.22* | 37.11 ± 0.25* | 37.22 ± 0.27* | 37.34 ± 0.29* | 37.46 ± 0.34* |
| OxSat, % | | | | | | | |
| | PLA | 58.8 ± 6.6 | 57.8 ± 6.9 | 57.8 ± 5.9 | 57.4 ± 5.1 | 56.5 ± 5.7 | 55.9 ± 5.4 |
| | POM | 62.9 ± 6.0 | 62.3 ± 6.2 | 61.7 ± 6.9 | 61.2 ± 7.4 | 60.5 ± 7.5 | 59.6 ± 7.6 |
| THC, µm | | | | | | | |
| | PLA | 64.2 ± 5.5 | 64.1 ± 5.3 | 64.1 ± 5.2 | 64.0 ± 5.7 | 64.4 ± 5.9 | 65.0 ± 5.2 |
| | POM | 66.7 ± 6.6 | 66.8 ± 6.1 | 66.8 ± 5.9 | 66.5 ± 5.3 | 66.8 ± 5.9 | 67.2 ± 5.7 |
| HbO, µm | | | | | | | |
| | PLA | 37.7 ± 4.7 | 37.0 ± 4.7 | 37.0 ± 4.2 | 36.6 ± 3.6 | 36.3 ± 4.5 | 36.3 ± 3.8 |
| | POM | 42.0 ± 6.1 | 41.6 ± 5.5 | 41.2 ± 5.8 | 40.7 ± 5.6 | 40.4 ± 6.3 | 40.0 ± 6.0 |
| HHb, µm | | | | | | | |
| | PLA | 26.5 ± 4.9 | 27.1 ± 5.2 | 27.1 ± 4.7 | 27.4 ± 4.6 | 28.1 ± 4.6* | 28.7 ± 4.6 |
| | POM | 24.7 ± 4.2 | 25.2 ± 4.6 | 25.6 ± 4.9 | 25.8 ± 5.3 | 26.4 ± 5.1 | 27.1 ± 5.4* |

Values are mean ± SD of 12 subjects for HR, Tcore, Tskin, and Tbody. Values are mean ± 11 subjects for VO2. Values are mean ± SD of 5 subjects for OxSat, THC, HbO, and HHb. Oxygen consumption (VO2), heart rate (HR), stroke volume (SV), cardiac output (Q), core temperature (Tcore), mean skin temperature (Tskin), body temperature (Tbody), muscle oxygen saturation (OxSat), total hemoglobin content (THC), oxygenated hemoglobin (HbO), and deoxygenated hemoglobin (HHb). * Indicates significant difference from previous value, $p < 0.05$.

## CHAPTER V: STUDY 2

## CARDIAC OUTPUT DURING INTENSE EXERCISE

**Abstract:**

Recent findings have challenged the traditional belief that the cardiac output (CO) and oxygen consumption (VO2) relationship is linear from rest to maximal exercise. The purpose of this study was to determine the CO and stroke volume (SV) response to a full range of exercise intensities. In order to integrate central and peripheral cardiovascular responses to exercise, near infrared spectroscopy was used to determine muscle deoxygenation (HHb) of two leg muscles, the vastus lateralis (VL) and the gastrocnemius (GAS). Ten well trained cyclists performed a series of discontinuous intervals to establish the CO vs. VO2 and the SV response to exercise across a wide range of exercise intensities (40 to 100% of VO2max). The increase in CO from 70 to 100% of VO2 was reduced when compared to the slope from 40 to 70% of VO2max (2.0 ± 0.4 vs. 4.4 ± 0.3 l/min, p = 0.025). CO did not increase significantly from 90 to 100% VO2max (23.9 ± 2.2 to 24.6 ± 2.6 l/min, p = 0.12). SV during high intensity exercise was reduced when compared to moderate intensity exercise (146.0 ± 16.6 vs. 138.5 ± 14.9 ml/beat, p = 0.015) whereas whole body arterial venous O2 difference (AVO2 difference) increased as intensity increased. The pattern of change in HHb was different between the VL and the GAS as VL-HHb plateaued at 80% of VO2max and GAS-HHb increased from 90 to 100% of VO2max. Overall, the increase in CO was attenuated as

exercise intensity increased as evidenced by the reduced rate of increase in CO per VO2 is reduced from 70 to 100% of VO2. At the micro-vascular level the pattern of muscle deoxygenation (~ O2 extraction) is different than the whole body (AVO2 difference).

**Introduction:**

The cardiac output (CO) vs. oxygen consumption (VO2) relationship is thought to be linear from rest to maximal exercise as CO is increased by 4 to 6 liters per minute for every 1 liter per minute increase in VO2 (Rowell, 1986). While this relationship may hold true for low and moderate intensity exercise (< 70 to 80% of VO2max), debate exists as to whether or not the same relationship can be applied to high intensity exercise.

Examination of the CO vs. VO2 relationship has been performed by either discontinuous interval exercise or incremental exercise from rest to VO2max. Typically, investigators utilizing a discontinuous exercise protocol measured CO and VO2 during a series of submaximal exercise intensities and then performed a bout of exercise at or near maximal intensity (Astrand *et al.*, 1964; Ekblom *et al.*, 1968; Ekblom & Hermansen, 1968). Linear regression of such data is biased towards the lower exercise intensities and therefore may not accurately portray the CO vs. VO2 relationship during high intensity exercise. Incremental exercise, in which a given workrate is performed for only a few minutes and a steady state is not achieved, may underestimate the true CO vs. VO2, especially at high levels of exertion and VO2.

Evidence for a reduced rate of increase in CO is most compelling from studies that have implemented an incremental protocol. Stringer et al. (Stringer *et al.*, 1997; Stringer *et al.*, 2005) used the direct Fick method to calculate CO and observed a linear relationship between AVO2 difference and VO2 and an attenuated increase in CO beginning at the lactic acidosis threshold. Similarly, Beck et al. (Beck *et al.*, 2006) used

the open circuit acetylene washin method to measure CO in a large sample of subjects (n = 73) and showed an attenuated increase in the CO vs. VO2 relationship which was most prominent in subjects with an above average fitness level. Mortensen et al. (Mortensen *et al.*, 2005) and Calbet et. al (Calbet *et al.*, 2007) showed that CO increased curvilinearly from rest to approximately 84% of maximal workrate and from 84 to 100% of maximal workrate the increase in CO was only 1.2L/min. However, the dynamic nature of the incremental exercise test may yield different results when compared to a protocol that establishes a steady state response. In support of a cardiac limitation to VO2max and maximal exercise is the finding that CO is reduced prior to fatigue during constant load maximal exercise (Gonzalez-Alonso & Calbet, 2003; Gonzalez-Alonso *et al.*, 2004; Mortensen *et al.*, 2005). This reduction in CO is due to a reduction in SV as HR is maintained at near maximal levels and leads to an impairment in systemic O2 delivery. Heat stress, resulting in an increased demand for the limited CO, accelerates fatigue and strengthens the argument in favor of CO limiting VO2max (Gonzalez-Alonso *et al.*, 2004).

In order to better understand and integrate the whole body response to a wide range of exercise intensities, near infrared spectroscopy (NIRS) was used in the present study to determine the muscle oxygenation status of two leg muscles (vastus lateralis and gastrocnemius) during exercise. Deoxygenated hemoglobin (HHb) is thought to be proportional to O2 extraction and the result of the relationship between oxygen delivery and oxygen consumption in the region of interest (Grassi *et al.*, 2003; Ferreira *et al.*,

2005b; Ferreira *et al.*, 2007). This technique coupled with whole body oxygen consumption has been used to gain insight into the matching of oxygen delivery, oxygen consumption, and blood flow during exercise (DeLorey *et al.*, 2003; Grassi *et al.*, 2003; Ferreira *et al.*, 2005b; Harper *et al.*, 2006; Ferreira *et al.*, 2007; Boone *et al.*, 2009).

The purpose of this study was to determine if the increase in CO is reduced at high exercise intensities. In order to answer this question, CO was measured during a series of discontinuous intervals across a wide range of exercise intensities (10% increments from 40 to 100% of VO2max). We hypothesized that as exercise intensity increases the rate of increase in CO per increase in VO2 would be reduced. In conjunction with this reduced rate of increase in CO we hypothesized that stroke volume would plateau during moderate intensity exercise and would be reduced during high intensity exercise. Regarding muscle deoxygenation, we hypothesized that HHb of the vastus lateralis and the gastrocnemius would increase linearly reflecting the linear increase in whole body AVO2 difference as exercise intensity is increased.

**Methods:**

*Subjects:* Ten healthy, well trained male cyclists (31 ± 8 yr of age, range 18 to 45) provided written informed consent to participate in this study. The protocol, experimental design, and informed consent form were approved by the Institutional Review Board at The University of Texas at Austin. The subjects' stature, body mass, and VO2max (means ± SD) were as follows: 1.79 ± 0.07m, 74.9 ± 7.9kg, 4.70 ± 0.33 l/min, respectively.

*Experimental design and protocol:* The entire experimental protocol was completed over 4 visits to the laboratory. The first visit served to establish the submaximal VO2 vs. workrate relationship, lactate threshold, and VO2max. The second visit was performed to familiarize the subject with the open circuit acetylene measurement and to verify that the workrates for the intervals were appropriate. Furthermore, a discontinuous VO2max protocol consisting of three high intensity intervals was performed during the second visit to ensure a true VO2max had been established. The third and forth visits to the laboratory involved moderate intensity (40, 50, 60, and 70% of VO2max) and high intensity intervals (80, 90, and 100%). Briefly, subjects performed the 40, 50, 60, and 70% intervals in sequential order and then performed the 80, 90, and 100% intervals in random order. Moderate intensity intervals were performed once per visit whereas high intensity intervals were performed twice per visit. This protocol yielded 4 measurements of CO per subject for each moderate intensity interval and 8 measurements of CO per subject for each high intensity interval.

The order of the high intensity intervals was randomized so as to not display an ordering effect and to remove the influence that fatigue may have on performance. Visits three and four were separated by one week and all experimental testing was performed at the same time of day.

*Experimental procedures:* Submaximal VO2 vs. workrate relationship was determined during a continuous incremental protocol on a cycle ergometer (Excalibur Sport, Lode, The Netherlands). Seat and handlebar position on the ergometer were matched to the subject's road bicycle and kept constant throughout the study. The submaximal test included 5 stages, each lasting 5 minutes. Workrate was progressively increased by 20 to 40 watts depending on the fitness level of the subject. Lactate samples were collected during the final minute of each stage by a finger stick and analyzed with a portable lactate meter (Lactate Pro, Arkray Inc, Kyoto, Japan). Lactate threshold (LT) was determined as the 1 mmol increase above baseline. Oxygen consumption (VO2) and HR were collected continuously during this test. VO2 was averaged over the final minute of each stage to determine the oxygen cost of cycling at each workrate. Following a 10 minute rest subjects performed an incremental VO2max test lasting 8 to 12 minutes. Initial workrate for the VO2max test was set to elicit approximately 80% of subject's reported maximal heart rate (HRmax). In order to verify a plateau in VO2max subjects rested again for 10 minutes before performing a constant load exercise bout at either the workrate they fatigued at during the incremental protocol or 25 watts higher than that workrate. The criteria for determining the

workrate during this VO2 verification trial depended on the duration of the final stage of the incremental test (Taylor *et al.*, 1955; Lafrenz *et al.*, 2008). If subjects lasted less than 1 minute during the final stage the same workrate was used for the constant load test. If subjects lasted longer than 1 minute during the final stage the workrate was increased by 25 watts for the constant load VO2 verification test. Average time to fatigue during the VO2 verification trial was 156 ± 28 seconds.

One week after initial testing, subjects returned to the laboratory for a second day of VO2max verification trials. This second day of testing was performed to determine if a true VO2max had been achieved during the first visit. Based on the submaximal VO2 vs. workrate relationship, linear regression was used to determine the minimal workrate needed to elicit VO2max. Following a 20 minute warm-up (5 minutes at 40, 50, 60, 70% of VO2max) subjects performed 3 high intensity intervals at 100%, 100% minus 25 watts (W), and 100% plus 25W of VO2max. Each interval was performed for 4 minutes or until exhaustion. Five minutes of passive recovery and 5 minutes of active recovery (easy spinning at 30W) separated the intervals. The order of the 100%, 100% minus 25W, and 100% plus 25W intervals was randomized. Using this method in combination with the incremental exercise test and constant load verification trials from visit one all subjects exhibited a clear leveling off of VO2 (i.e.; a true VO2max).

Visits three and four consisted of interval cycling at 40, 50, 60, 70, 80, 90, and 100% of VO2max. Each submaximal stage (i.e.; 40 – 70% VO2max) lasted 5 minutes and was separated by 6 minutes of cycling at 30W. The high intensity intervals (i.e.; 80 –

100% of VO2max) were performed for 4 minutes and separated by 6 minutes of cycling at 30W (similar to unloaded cycling). Breath by breath VO2 measurements commenced at least 2 minutes prior to each interval, cardiac output was measured at min 3 and 4.5 of each submaximal stage and at min 2 and 3.5 of each high intensity interval. The 1.5 minute time period between CO measurements was selected based on pilot data that showed adequate washout of acetylene. CO was not measured during the primary phase of VO2 response.

Approximately 30 minutes prior to exercise subjects consumed 400 ml of water. During exercise subjects drank a 6% CHO-electrolyte beverage (Powerbar Endurance Formula, Nestle). Subjects were allowed to drink *ad libitum* during visit 3. Fluid intake (timing and volume) were recorded and matched during visit 4. On average, 1.2 ± 0.3 L of fluid was consumed. The overall change in bodyweight from pre to post exercise was less than 0.25 kg indicating that hydration was maintained.

On arrival, subjects dressed in cycling shorts and shoes. Before testing commenced on visits two, three and four, subjects inserted a rectal temperature probes and voided their bladder. A subset of subjects (n = 7) inserted an esophageal temperature probe. Following probe placement, subjects were instrumented and resting measures were made. After all baseline measures were made subjects performed the series of intervals as previously described.

*Respiratory and cardiovascular measurements:* Oxygen consumption was measured breath by breath using open-circuit spirometry according to the calculation described by Beaver et al. (Beaver *et al.*, 1981). Subjects breathed through a two-way non rebreathing valve connected to a pneumotachometer (Hans Rudolph, Kansas City, MO). Oxygen and carbon dioxide concentration of inspired and expired gases were determined by a mass spectrometer (Perkin-Elmer MGA 1100, St. Louis, MO). Gas samples were collected at the mouthpiece via a 6 foot capillary tube connected directly to the mass spectrometer. CO was determined by open circuit acetylene washin as described by Johnson et al. (Johnson et al., 2000). Briefly, at the end of normal expiration, the participants breathed for a minimum of 8 breaths through a mouthpiece connected to a bag filled with mixed gases, including 0.7% acetylene, 9.0% helium, 21% oxygen, and balance nitrogen. The concentrations of acetylene and helium were monitored by continuous sampling at the mouthpiece and data was viewed in real time on a personal computer. CO was calculated from the washin curve of the acetylene according to a single alveolar one compartment lung model. The iterative method as described by Johnson et al. (Johnson et al., 2000) was used for the calculation of CO. Custom software (Beck Integrated Physiological Systems) was used to determine breath by breath oxygen consumption and to calculate CO. The mass spectrometer was calibrated prior to each experimental trial using gases of known concentration. Volume was calibrated using a 3 l syringe (Hans Rudolph) at low, moderate, and high flow rates.

Heart rate was measured continuously (Physioflow) and average HR corresponding the CO measurement was used for the calculation of SV (SV = CO/HR).

*Core body temperature:* Core temperature (Tcore) was measured using a rectal temperature probe inserted 12 cm past the anal sphincter (model 401, Yellow Springs Instrument). A subset of subjects (n = 7) also performed esophageal core temperature measurements (Teso). The esophageal probe (model 4491, Yellow Springs Instruments) was inserted through the nasal passage and swallowed to depth of one-fourth of the subject's standing height (Mekjavic & Rempel, 1990). As stated earlier, fluid was consumed prior to and during exercise (i.e.; between intervals). In order to not affect the Teso measurements all subjects consumed fluid that was warmed to approximately 37$^{o}$C.

*Near Infrared Spectroscopy (NIRS):* Muscle oxygenation was evaluated by a frequency-domain multi-distance NIRS system (Oxiplex TS, ISS, Champaign, IL). The principles of operation and algorithms used by this NIRS system have been previously described (Gratton et al., 1997). For this experiment two NIRS probes were positioned longitudinally on the belly of the vastus lateralis approximately 12 cm above the lateral border of the patella and the other on the belly of the lateral head of the gastrocnemius. The probe was held in place by a Velcro strap provided by the manufacturer. A latex glue (Skin Bond®) was used to adhere the probe to the skin and to reduce movement of the probe during exercise. The subject's cycling shorts were pulled over the quadriceps probe and a spandex sleeve was placed over the calf probe to

further minimize movement of the probes. The NIRS system was calibrated prior to each test after a warm-up of at least 30 minutes. The calibration was done with the optical probe placed on calibration block with absorption and reduced scattering coefficients previously measured and correction factors were determined and automatically implemented by the equipment's software for the calculation of the absorption coefficient (μa) and reduced scattering coefficient (μs) for each wavelength during the data collection. The NIRS system provides a continuous measurement of absolute concentration of oxyhemoglobin ([HbO2], and deoxyhemoglobin ([HHb]) (expressed in μM). The HHb reported in the present study was calculated incorporating the continuous measurement of μs made throughout the exercise test, i.e.; without assuming a constant for scattering. NIRS data was exported from the manufacturer's software at 1 Hz to provide second by second data. Baseline HHb was obtained during 30W cycling. The final HHb value was the average of the final 30 seconds of each interval. The change in HHb was calculated and then normalized using the following equation; % HHb = [(value of interest – min)/(max – min)] *100 (Belardinelli et al., 1995). Due to technical problems in one subject, HHb is reported for 9 subjects.

*Statistics:* All statistical analyses were performed using SPSS version 14.0. Data are presented as mean ± standard deviation of the mean. Selected figures are presented as mean ± standard error for the purpose of clarity. A one-way repeated measures ANOVA analysis was used to test for significant differences between exercise intensities. When appropriate, an *a priori* analyses of sequential exercise intensities (40% to 50%,

50% to 60%, 60% to 70%, 80% to 90%, or 90% to 100% of VO2max) was employed following a significant main effect of condition. The number of *a priori* comparisons was limited to k-1 for the selected variable, where k is equal to the number of means compared. If Mauchly's test of sphericity was violated, the Greenhouse-Geisser correction was used to correct for this violation and to ensure that the main effect was significant. All non-sequential pairwise comparisons were corrected using the Sidak correction for multiple comparisons (i.e.; 40% to 60% or 80% to 100% of VO2max). Significance was accepted at the $P < 0.05$ level.

**Results:**

*Workrate, exercise intensity and ventilation:* Exercise was performed at workrates eliciting 42, 51, 60, 70, 83, 91, and 99% of VO2max. For the purpose of clarity further discussion of the aforementioned intervals will be referred to as 40, 50, 60, 70, 80, 90, and 100% of VO2max. Absolute VO2 and corresponding workrates are reported in Table 2.1. Ventilation increased in an exponential manner as intensity increased. During high intensity exercise, the increase in VE per increase in VO2 was approximately twice as great during high intensity (56 l/min per 1 l/min) exercise compared to low and moderate intensity exercise (27.7 l/min per 1 l/min) (Table 2.1).

*Cardiovascular responses:* HR for each interval is reported in Table 2.2. Each increase in workrate was accompanied by a significant increase in HR with one exception. The random order of the intervals elevated HR at 80% thereby making the difference between 80 and 90% not significant ($p = 0.87$) despite the 41 watt and 0.299 LO2/min difference between the stages.

From rest to 70% of VO2max the increase in CO vs. VO2 was 5.0 ± 0.4 l/min. However, for the purpose of comparing slopes, only values during exercise were analyzed. The slope of the CO vs. VO2 relationship was significantly reduced as exercise intensity increased (Figure 2.2). The slope of CO vs. VO2 from 70 to 100% VO2max was significantly reduced when compared to the slope from 40 to 70% of VO2max (2.0 ± 0.4 vs. 4.4 ± 0.3 l/min, $p = 0.025$). The CO values for each workrate are reported in Table 2.2.

CO increased significantly from one workrate to the next until 90% of VO2max (Figure 2.1). The increase in CO from 90 to 100% of VO2max was not significant (23.9 ± 2.2 to 24.6 ± 2.6 l/min, $p = 0.12$). The reduced increase in CO vs. VO2 at high exercise intensities coupled with the non-significant increase from 90 to 100% of VO2 max indicates a CO limitation during high intensity exercise.

The SV response to exercise is reported in Table 2.2. SV increased significantly from rest to exercise (112.0 ± 20.5 to 138.6 ± 17.3 ml/beat, $p < 0.01$) and again from 40 to 50% VO2max (138.6 ± 17.2 to 144.8 ± 17.2ml/beat, $p < 0.01$). SV peaked at 70% of VO2max (147.8 ± 15.9) and was reduced by approximately 7% ($p < 0.05$) at 80% and 100% of VO2max. SV was not different from 50% to 70% or from 80% to 100% and when pooled together the SV was significantly lower during high intensity exercise (80, 90, and 100% of VO2max) compared to moderate intensity exercise (50, 60, and 70% of VO2max) (138.5 ± 14.9 vs. 146.0 ± 16.6 ml/beat, $p = 0.015$).

AVO2 difference increased as exercise intensity increased with the only exception being from 40% to 50% of VO2max. AVO2 difference is reported in Table 2.2. The slope of the AVO2 difference from 70 to 100% of VO2max was slightly higher than the slope from 40 to 70% of VO2max; however, this difference was not significant (2.9 ± 1.1 vs. 2.0 ± 1.0 ml/dl, $p = 0.14$).

*Core temperature:* From 40 to 70% of VO2max Tcore increased on average 0.24$^{o}$C per stage ($p < 0.05$) (Table 2.1). Tcore was elevated during maximal exercise:

however, there were no differences between 80, 90, and 100% VO2max. In order to verify that the rectal temperature measurement was able to accurately measure the change in core temperature during the brief bouts of high intensity exercise (4 min), esophageal temperature was measured in conjunction with the rectal temperature measurement in 7 of the 10 subjects. Rectal temperature was significantly lower at rest and 40% of VO2max compared to esophageal temperature; however, there were no significant differences between the two methods from 50 to 100% of VO2max (APPENDIX I: Table 2.4 Rectal vs. Esophageal core temperature measurements)

*Muscle deoxygenation:* Prior to the start of each interval (ie; during 30W cycling), HHb was not different between exercise intensities for either the vastus lateralis (VL) or the gastrocnemius (GAST) (Table 2.3). There were no significant increases in normalized VL-HHB (% VL-HHb) beyond 80% of VO2max, indicative of a plateau in oxygen extraction for the vastus lateralis. In contrast, normalized GAST-HHb (% GAST-HHb) showed a significant increase from 90 to 100% of VO2 ($p = 0.037$) (Figure 2.3). Given that HHb approximates tissue O2 extraction, this finding has direct implications regarding muscle specific differences in O2 extraction and blood flow during cycle exercise. A qualitative analysis of Qcap revealed that Qcap-VL continued to increase as exercise intensity increased, whereas Qcap-GAST plateaued at 90% of VO2max (Figure 2.4).

**Discussion:**

The main finding of the present study was that during moderate to high intensity exercise (70 to 100% VO2max) the slope of the CO vs. VO2 relationship is reduced when compared to the slope from low to moderate exercise (40 to 70% VO2max) (2.0 ± 0.4 vs. 4.4 ± 0.3 l/min, p =0.025). Furthermore, CO only increased by 1.5 l/min from 80 to 100% of VO2max, a finding similar to what has been reported for incremental exercise (Mortensen *et al.*, 2005; Calbet *et al.*, 2007). Another main finding of the study was that SV plateaued at approximately 50% of VO2max and was reduced during high intensity exercise when compared to low and moderate intensity exercise. The attenuated increase in the CO to VO2 relationship coupled with the plateau and decline in SV provides strong evidence to support the concept of a cardiac limitation to high intensity exercise (Gonzalez-Alonso & Calbet, 2003; Mortensen *et al.*, 2005; Beck *et al.*, 2006; Saltin *et al.*, 2006; Gonzalez-Alonso, 2008b). An additional novel finding was that the pattern of change in deoxygenated HHb (approximated O2 extraction) was different between the vastus lateralis and the gastrocnemius during upright cycle exercise. The vastus lateralis exhibited a plateau in HHb from 80 to 100% of VO2max whereas the gastrocnemius showed a significant increase in HHb at 100% VO2max. This finding has possible implications regarding capillary blood flow heterogeneity to the muscles of the leg during cycling exercise.

Previous investigations have found a curvilinear or reduced increase in the CO to VO2 relationship (Bevegard *et al.*, 1963; Astrand *et al.*, 1964; Hanson & Tabakin, 1965; Grimby *et al.*, 1966; Ekblom & Hermansen, 1968; Hermansen *et al.*, 1970; Stringer *et al.*, 1997; Stringer *et al.*, 2005; Beck *et al.*, 2006). However, the majority of these studies used incremental ramp exercise (Stringer *et al.*, 1997; Mortensen *et al.*, 2005; Stringer *et al.*, 2005; Beck *et al.*, 2006; Calbet *et al.*, 2007) while those that did implement steady state discontinuous exercise typically measured CO during 1 to 4 submaximal work bouts and then again at maximum (Astrand *et al.*, 1964; Grimby *et al.*, 1966; Ekblom & Hermansen, 1968). The present study is the only study to date that implemented a series of high intensity steady state intervals to assess the CO vs. VO2 relationship. The use of interval exercise of at least 4 minutes in duration allowed us to make duplicate measures of CO at each intensity after the primary phase of the VO2 response was complete. While a slow VO2 component was present during our measures of CO, the majority (approximately 86%) of this slow component is caused by factors arising in the exercising legs (Poole *et al.*, 1991; DeLorey *et al.*, 2003; Ferreira *et al.*, 2005a). Previous studies that used discontinuous interval type exercise to determine CO generally only performed a few bouts of exercise at submaximal intensities and a final bout at near maximal or maximal intensity (Bevegard *et al.*, 1963; Astrand *et al.*, 1964). This type of protocol cannot assess the CO to VO2 relationship at high intensities as only one measure of CO was made at maximal workrates. The focus of the present study was to measure CO over a wide range of intensities with special attention to workrates greater

than 80% VO2max. Due to the dynamic non-steady state nature of incremental exercise measures of CO and VO2 may not be generalized to steady state exercise (Stringer *et al.*, 2005). Other studies that have shown a reduction in CO at maximal effort made CO measurements just prior to fatigue when cardiovascular function was at its limit (Gonzalez-Alonso & Calbet, 2003; Gonzalez-Alonso *et al.*, 2004; Mortensen *et al.*, 2005; Mortensen *et al.*, 2008). While a reduction in SV and subsequent drop in CO prior to exhaustion argues in favor of a cardiac limitation to maximal exercise (Gonzalez-Alonso & Calbet, 2003; Mortensen *et al.*, 2005; Beck *et al.*, 2006; Saltin *et al.*, 2006; Gonzalez-Alonso, 2008b, a; Warburton & Gledhill, 2008b, a) it does not add to the description of the overall CO to VO2 relationship from rest to maximal exercise.

Establishing the CO vs. VO2 relationship across a wide range of exercise intensities is important as this approach allows for the determination of when the attenuated increase in CO begins to manifest. As discussed by Beck et al. (Beck *et al.*, 2006) if the attenuation in CO becomes more pronounced (i.e.; a more prominent negative curvature in the CO vs. VO2 relationship) with exercise training a mechanical cardiac limitation would be suggested. Similarly investigating the CO vs. VO2 relationship in individuals with a known cardiac limitation may be insightful as the shape of the CO vs. VO2 relationship would depend on how well the cardiac pump could increase SV as HR and venous return increase but filling time decreases (Beck *et al.*, 2006). From a practical perspective, most competitive endurance events occur at intensities above 70% of VO2max and based on the results of this study the reduction in

the slope of CO vs. VO2 begins at approximately 70% of VO2max. The malleability of this relationship through exercise training is not known and is worthy of future investigation.

It is important to address the manner in which CO was measured in the current study in order to be certain that the reduction in CO is not an artifact of the open circuit acetylene washin technique. The open circuit acetylene washin method for determining CO has been compared with thermodilution in anesthetized and ventilated dogs, the acetylene rebreathing technique in humans, and the direct Fick method in humans during submaximal and maximal exercise (Stout *et al.*, 1975; Gan *et al.*, 1993; Nielsen *et al.*, 1994; Johnson *et al.*, 2000). As addressed by Johnson et al. (Johnson et al., 2000), ventilation inhomogeneity and ventilation-to-perfusion ratio mismatching will cause CO and lung volumes to be underestimated when using the open circuit or any rebreathing technique. The open circuit technique is clearly dependent on the ventilation-to-perfusion ratio and is not appropriate to measure CO in individuals with pulmonary disease (Kallay *et al.*, 1987). This precaution was not a factor in the present study as all subjects were healthy and free of pulmonary disease. Another factor that could potentially contribute to an underestimation of CO when using the open circuit method or any ventilatory dependent method for assessing CO is the presence of anatomic shunts. However, studies (Hopkins et al., 1998; Hopkins et al., 2008) using the multiple inert gas technique have shown that such an intrapulmonary shunt is always less than 1 % of CO.

Another often debated topic focusing on the central limitation to exercise is the manner in which SV responds to increasing exercise intensity (Vella & Robergs, 2005). Classic studies by Bevegard et al. (Bevegard *et al.*, 1963) and Astrand et al. (Astrand et al., 1964) showed an initial increase in SV from rest to upright exercise and then a constant SV from moderate to maximal exercise, a finding that has been repeated numerous times (Higginbotham *et al.*, 1986; Flamm *et al.*, 1990; Seals *et al.*, 1994; Stringer *et al.*, 1997; Proctor *et al.*, 1998; McCole *et al.*, 1999; Gonzalez-Alonso & Calbet, 2003; Gonzalez-Alonso *et al.*, 2004; Stringer *et al.*, 2005). The present study supports this finding as SV did not increase beyond 50% of VO2max. Furthermore, the 10 ml/beat reduction in SV at high intensity exercise as observed in the present study is partially responsible for the reduced increase in CO as HR continued to increase as intensity increased. Previous investigations have found a reduction in SV at peak exercise during both constant load and incremental exercise in well trained endurance athletes and moderately trained individuals (Flamm *et al.*, 1990; Spina *et al.*, 1992; Seals *et al.*, 1994; Mortensen *et al.*, 2005; Stringer *et al.*, 2005). A fortuitous finding of the present study was the elevation in HR during the 80% VO2max interval and the outcome that this tachycardia had on SV. Due to the randomized design of the intervals, the HR during the 80% interval was elevated and only 3 bpm lower than the 90% interval. Despite this elevation in HR, CO and VO2 were appropriate (i.e.; linear increase in VO2 with workrate). Therefore, the tachycardia associated with this workrate resulted in a reduced SV, most likely due to a reduction in diastolic filling time and reduced end

diastolic volume presumably due to a lower left ventricular filling pressure when compared to the higher workload interval (Fritzsche *et al.*, 1999).

The plateau and reduction in SV during high intensity exercise is a finding that has not been corroborated by all investigators. Other investigators have found that SV in highly trained individuals continues to increase as exercise intensity increases and that almost all endurance athletes achieve their highest SV during maximal exercise while untrained or moderately trained individuals exhibit a plateau or drop in SV at peak exercise (Gledhill *et al.*, 1994; Vella & Robergs, 2005; Warburton & Gledhill, 2008b, a). The reason for the continual increase in SV is thought to be due to improved diastolic function as the result of chronic exercise training (Gledhill et al., 1994). Recent work by Faisal et al. (Faisal et al., 2009) examined the SV kinetic response to moderate and high intensity exercise and found that SV exhibits a substantial overshoot during the first few minutes of exercise and then decreases and eventually levels off as exercise duration progresses. The manner in which cardiac function is determined (HR matched vs. VO2 matched) and the timing of the CO and SV measurement coupled with the protocol employed (incremental vs. discontinuous, short duration maximal or supramaximal effort) may confound the SV finding and lead to overestimation of CO and SV. The low maximal (a-v)O2diff ( < 130 ml/l) observed by Gledhill et al. (Gledhill et al., 1994) may also explain the overestimated Q and SV measurements. Furthermore, maximal CO as measured by Gledhill et al. (Gledhill *et al.*, 1994) was 34.8 l/min at a VO2 of 4.4 l/min. A similar CO (36 l/min) was observed by Ekblom and Hermansen (Ekblom & Hermansen,

1968) in elite athletes; however, the corresponding VO2 was much higher at nearly 6.2 L/min.

Near infrared spectroscopy provides a noninvasive measure of muscle oxygenation (or O2 extraction) in the microcirculation (Grassi *et al.*, 2003; DeLorey *et al.*, 2005; Ferreira *et al.*, 2005b; Harper *et al.*, 2006; Ferreira *et al.*, 2007; Boone *et al.*, 2009). Furthermore, although the muscle oxygenation signal from NIRS does not allow for specific assessment of intracellular oxygenation, the HHb is the result of the relationship between oxygen delivery and oxygen consumption in the region of interest (Grassi 2003). Therefore, as the NIRS originates in the microcirculation (Liu *et al.*, 1995), HHb is considered to reflect the balance between muscle oxygen consumption and blood flow at the capillaries (DeLorey *et al.*, 2003; Grassi *et al.*, 2003; DeLorey *et al.*, 2004b, a, 2005; Ferreira *et al.*, 2005a; Ferreira *et al.*, 2005b; Ferreira *et al.*, 2006; Harper *et al.*, 2006; Ferreira *et al.*, 2007; Boone *et al.*, 2009). Although not well understood, the slow component of the HHb signal most likely resembles a muscle response, given that approximately 86% of the pulmonary VO2 slow component arises from the active muscle (Poole *et al.*, 1991; Grassi *et al.*, 2003; Ferreira *et al.*, 2005a). NIRS cannot distinguish between the myoglobin (Mb) and hemoglobin (Hb) signal; however, the Mb contribution appears to be minimal and contribute less than 10% to the total signal in humans. Furthermore, the deoxygenated Mb signal did not change from 50 – 60% to 100% of work max (Richardson et al., 1995), whereas the HHb continued to increase up to VO2max (Grassi et al., 1999). Given that the Mb signal is less than 10% of the total

signal and changes little from 50 to 100% of VO2 max, the HHb appears to be a reasonable estimate of O2 extraction (Seiyama *et al.*, 1988; McCully & Hamaoka, 2000).

The present study is the first, to our knowledge, to examine HHb in two leg muscles during cycling exercise. The vastus lateralis is commonly measured with NIRS as this muscle is the primary contributor to force production during upright cycling. However, other muscle groups of the lower body (gluteus, hamstrings, and calf muscles) are recruited and contribute to force production and joint stabilization during cycling (Dingwell *et al.*, 2008). Based on the findings of this study, the vastus lateralis and gastrocnemius exhibited somewhat different patterns of muscle deoxygenation during cycling exercise. The vastus displayed a plateau in HHb starting at approximately 80% of VO2max with no increase from 90 to 100%. A similar pattern of vastus HHb has been seen during incremental exercise while cycling (Ferreira *et al.*, 2007; Boone *et al.*, 2009). The gastrocnemius, however, showed an increase in HHb from 90 to 100%. Given that HHb resembles O2 extraction this finding indicates that the pattern of O2 extraction also differs in leg muscles during cycling. This dissimilar pattern in HHb (Figure 2.3) has implications for blood flow distribution to the active muscle during cycling. Capillary blood flow (Qcap) to the vastus lateralis has been estimated during cycling by using HHb (~ O2 extraction) and VO2 during cycling. Based upon the findings of the current study and the data presented on highly trained cyclists (Boone *et al.*, 2009), the rate of Qcap to VO2 appears to increase from approximately 90 to 100% of maximal workrate (Wmax) at least the in microcirculation near the vastus lateralis. Despite the difference

in protocols (discontinuous vs. incremental ramp) between Boone et al. (Boone *et al.*, 2009) and the present study the Qcap to muscle VO2 (pulmonary VO2 used as a surrogate for muscle VO2, (Ferreira *et al.*, 2007; Boone *et al.*, 2009)) relationship appears similar. Based on the different HHb response between the VL and GAST the inferred Qcap to VO2m relationship for the VL and GAST was markedly different from 90 to 100% of VO2max as Qcap for the VL increased from 90 to 100% whereas Qcap for GAST plateaued at 90% of VO2max (Figure 2.4). This difference between the Qcap to VO2m relationship for the two muscle groups may indicate that the blood flow to the smaller muscle group (gastrocnemius) does not increase from 90 to 100% of VO2max whereas blood flow to the primary muscle of force production (vastus lateralis) continues to increase up to 100% of VO2max. We are unaware of any studies that have made direct measurements of vastus lateralis and gastrocnemius oxygen consumption and blood flow during cycling as this would require isolation of venous outflow from the respective muscle beds. The observed differences in muscle deoxygenation and estimated Qcap may be explained by differences in mean transit time, diffusing area, and diffusing distance, in small verse large muscle groups (Calbet *et al.*, 2005). This interpretation must be made with caution as the assumption is made that VO2m increases to the same degree in both the gastrocnemius and vastus lateralis during cycling exercise.

By revisiting a classic topic in exercise physiology new insights regarding limitations to high intensity exercise have been gained. The increase in CO was

attenuated as exercise intensity increased beyond 70% of VO2max. Furthermore, SV plateaued during moderate intensity exercise and was reduced at high intensity exercise. Whole body AVO2 difference continued to increase as exercise intensity and VO2 increased, however, at the level of the microcirculation, oxygen extraction at the vastus lateralis plateaued during high intensity exercise which has direct implications regarding the balance of muscle oxygen uptake and blood flow control.

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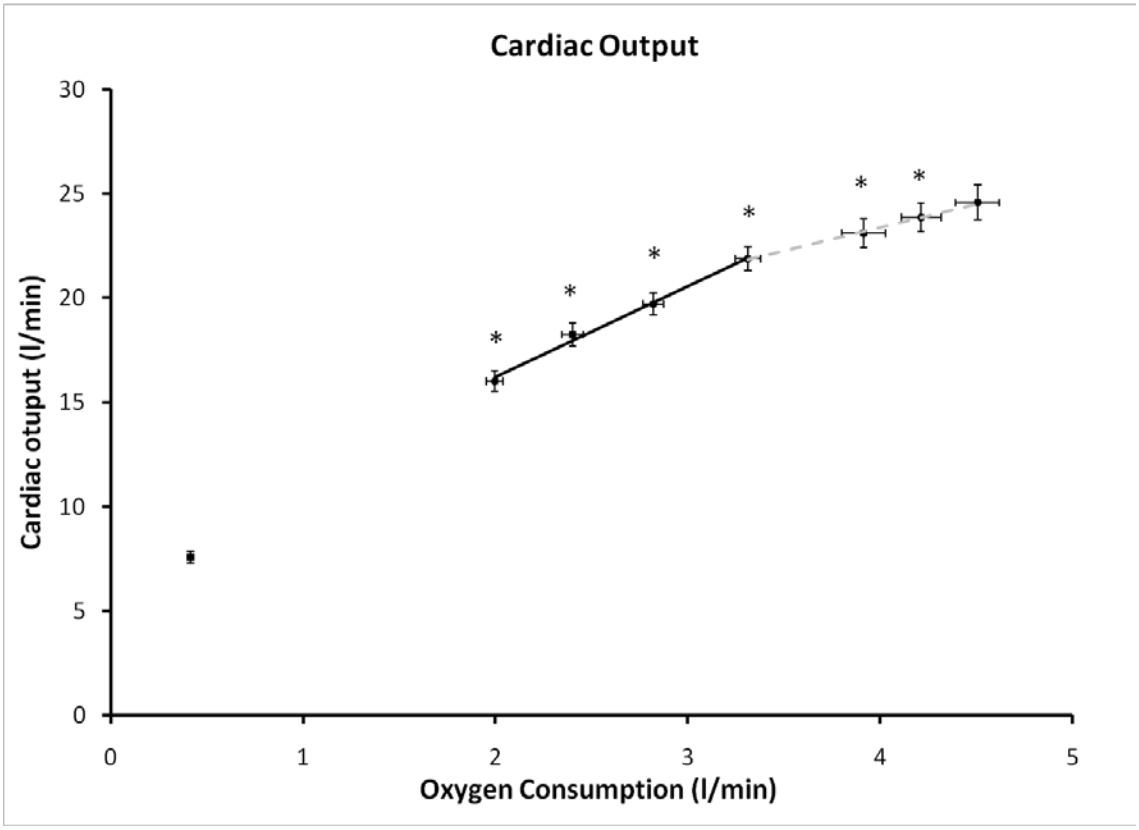


Figure 2.1: Values are mean ± SE of 10 subjects. * Indicates significant difference from previous value, $p < 0.05$.

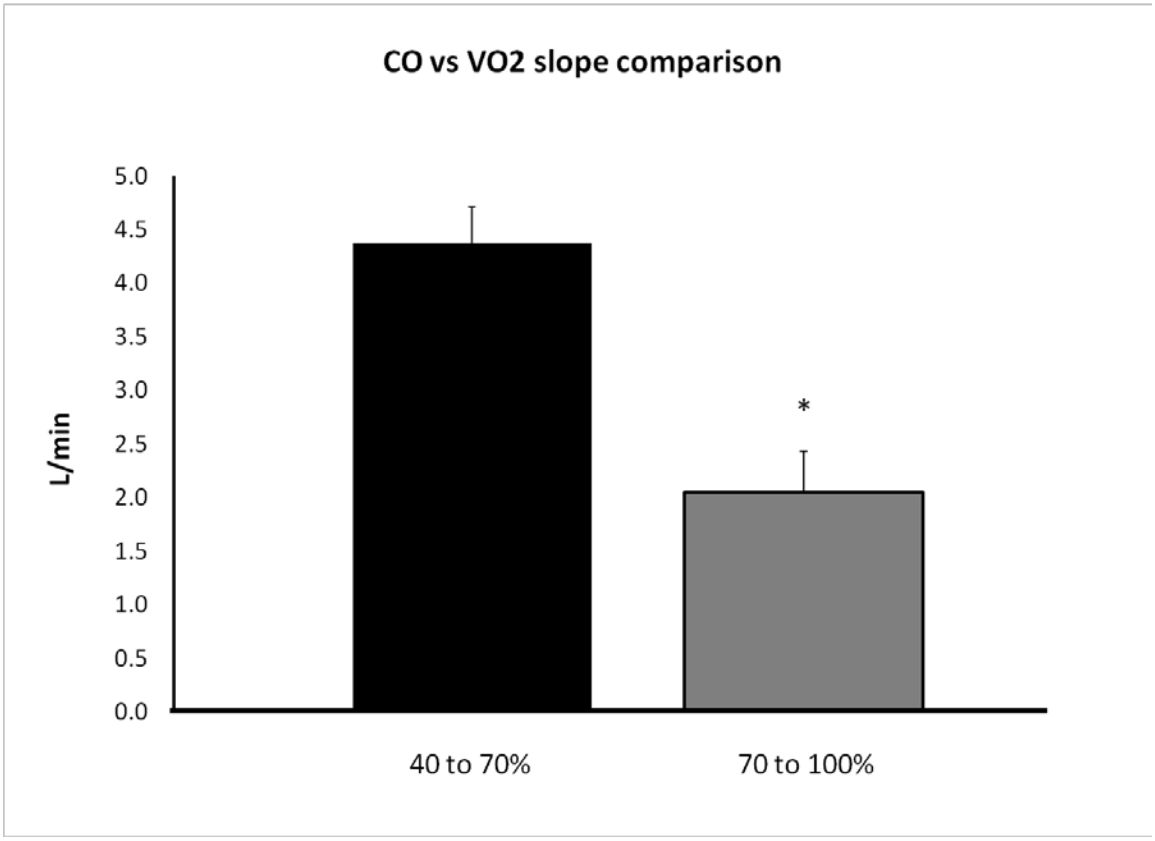


Figure 2.2: Values are mean ± SE of 10 subjects. Slope was determined from each individual Q vs. VO2 relationship. * Indicates significant reduction in slope from 40 to 70% of VO2max, $p < 0.05$.

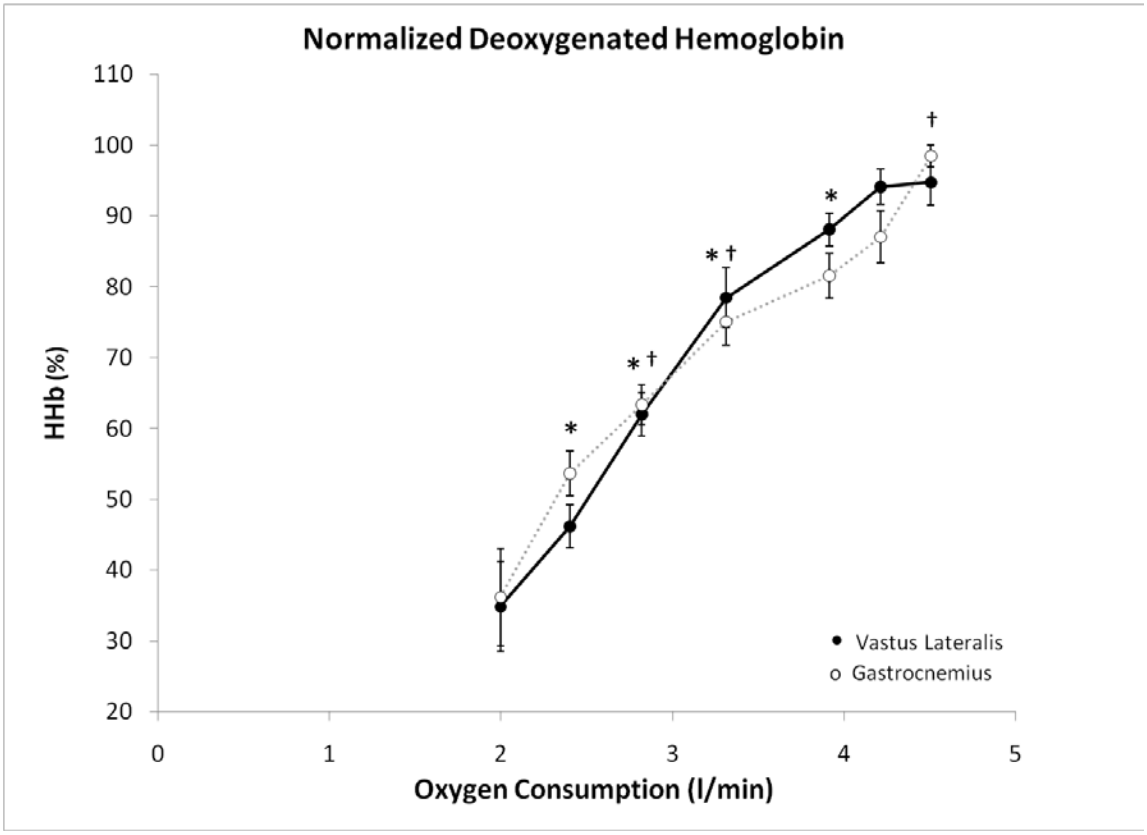


Figure 2.3: Values are means ± SE of 9 subjects. Closed circles (•) represent vastus lateralis (VL) and open circles (o) represent gastrocnemius (GAST). Normalized deoxygenated hemoglobin (HHb) was calculated based on the change in HHb from baseline 30W cycling to the HHb value obtained during the final 30 seconds of each workrate. Peak HHb was determined for each subject and then converted to 100%. The following equation was used for the calculation of % HHb; % HHb = [(value of interest – min)/(max – min)] *100 (Belarandani et al). * Indicates significant increase from previous value for VL, † indicates significant difference from previous value for GAST, $p < 0.05$.

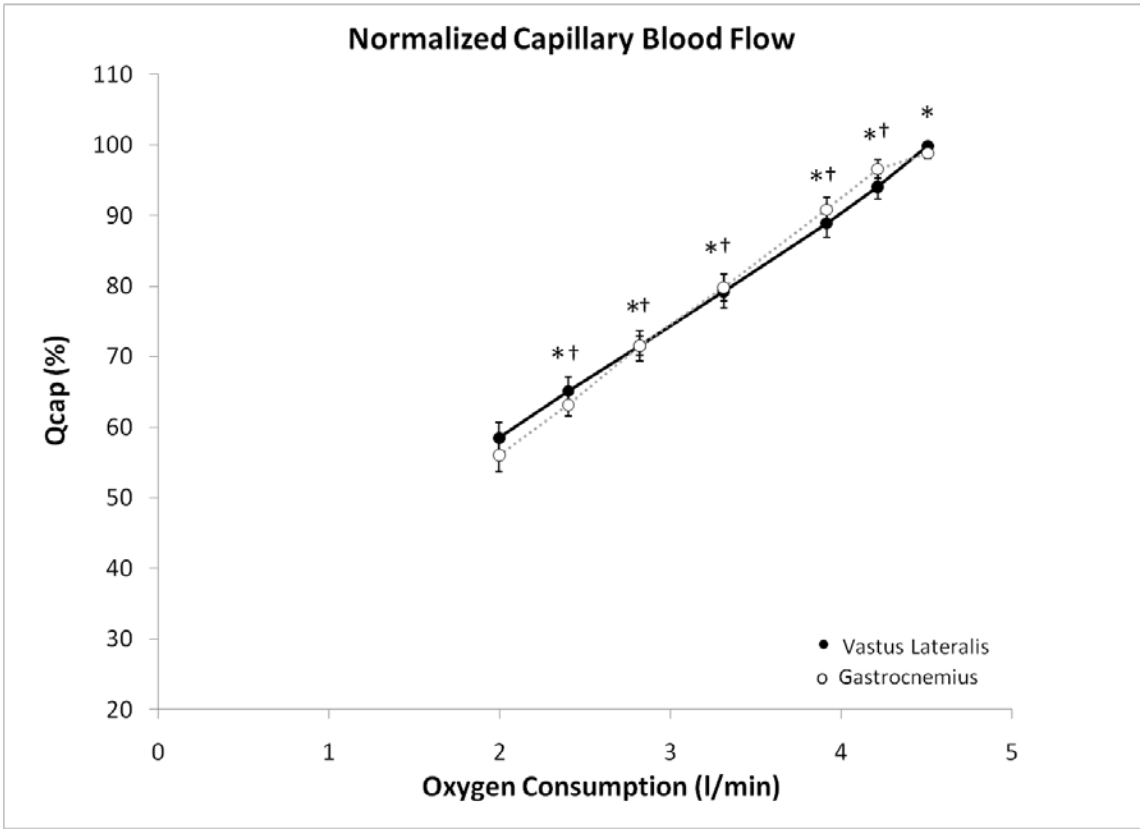


Figure 2.4: Values are means ± SE of 9 subjects. Closed circles (•) represent vastus lateralis (VL) and open circles (o) represent gastrocnemius (GAST). Qcap was calculated in a qualitative way by solving the Fick equation in which deoxygenated hemoglobin (HHb) was used as an expression of (a-v)O2 difference and pulmonary VO2 as surrogate of muscle VO2 (VO2m). Normalized capillary blood flow (Qcap) was calculated based on the change in HHb from baseline 30W cycling to the HHb value obtained during the final 30 seconds of each workrate. Peak HHb was determined for each subject and then converted to 100%. The following equation was used for the calculation of % Qcap; % Qcap = [(value of interest – min)/(max – min)] *100 (Belarandani et al). * Indicates

significant increase from previous value for VL, † indicates significant difference from previous value for GAST, $p < 0.05$.

Table 2.1: Exercise intensity, respiratory, and core temperature responses to exercise

| | Rest | 40% | 50% | 60% | 70% | 80% | 90% | 100% |
|---|---|---|---|---|---|---|---|---|
| Workrate, watts | 0 ± 0 | 132 ± 15* | 174 ± 18* | 216 ± 23* | 257 ± 27* | 300 ± 31* | 341 ± 35* | 383 ± 38* |
| VO2, l/min | 0.416 ± 0.050 | 1.997 ± 0.140* | 2.402 ± 0.176* | 2.821 ± 0.175* | 3.312 ± 0.212* | 3.914 ± 0.356* | 4.213 ± 0.330* | 4.507 ± 0.360* |
| % VO2max | 9 ± 1 | 42 ± 3 | 51 ± 3 | 60 ± 2 | 70 ± 3 | 83 ± 4 | 91 ± 2 | 99 ± 1 |
| VE, l/min | 15.6 ± 3.0 | 49.1 ± 4.9* | 59.3 ± 6.1* | 70.4 ± 7.7* | 85.5 ± 10.8* | 115.0 ± 21.1* | 128.9 ± 16.6* | 148.3 ± 17.9* |
| Rectal Tcore, $^{o}$C | 37.23 ± 0.27 | 37.24 ± 0.25 | 37.43 ± 0.23* | 37.68 ± 0.22* | 37.87 ± 0.22* | 38.20 ± 0.27* | 38.17 ± 0.28 | 38.26 ± 0.28 |

Values are mean ± SD of 10 subjects. Percent of workrate maximum (% Wmax), O2 consumption (VO2), percent of maximal O2 consumption (% VO2max), ventilation (VE), and core temperature (Tcore). % VO2max was calculated using the final 30 second average for each workrate. * Indicates significant increase from previous value, $p < 0.05$.

Table 2.2: *Cardiovasuclar reponses to exercise*

| | Rest | 40% | 50% | 60% | 70% | 80% | 90% | 100% |
|---|---|---|---|---|---|---|---|---|
| HR, bpm | 69.5 ± 12.7 | 116.2 ± 9.2* | 126.7 ± 10.6* | 136.5 ± 11.3* | 148.7 ± 10.1* | 168.2 ± 8.2* | 171.2 ± 8.2 | 179.1 ± 9.0* |
| % HRmax | 37.3 ± 6.6 | 62.4 ± 4.7* | 68.0 ± 5.1* | 73.3 ± 5.3* | 79.8 ± 4.3* | 90.3 ± 3.3* | 91.9 ± 3.2 | 96.1 ± 3.3* |
| CO, l/min | 7.6 ± 0.9 | 16.0 ± 16* | 18.2 ± 1.8* | 19.7 ± 1.7* | 21.9 ± 1.8* | 23.1 ± 2.2* | 23.9 ± 2.2* | 24.6 ± 2.6 |
| SV, ml/beat | 112.0 ± 20.5 | 138.6 ± 17.3* | 144.8 ± 17.2* | 145.3 ± 17.5 | 147.8 ± 15.9 | 137.9 ± 15.5† | 139.9 ± 14.9 | 137.7 ± 16.2† |
| AVO2diff, ml/dl | 5.6 ± 0.8 | 12.7 ± 1.4* | 13.2 ± 1.0 | 14.4 ± 0.9* | 15.2 ± 1.1* | 17.1 ± 1.6* | 17.7 ± 1.2* | 18.5 ± 1.3* |

Values are mean ± SD of 10 subjects. Heart rate (HR), percent of heart rate maximum (% HRmax), cardiac output (Q), stroke volume (SV), aterial-venous O2 difference (AVO2diff). * Indicates significant difference from previous value, † indicates significant decrease from 70%, $p < 0.05$.

Table 2.3: *Baseline and normalized deoxygenated hemoglobin for vastus lateralis and gastrocnemius*

| | 40% | 50% | 60% | 70% | 80% | 90% | 100% |
|---|---|---|---|---|---|---|---|
| BL VL-HHb, µm | 35.14 ± 8.49 | 34.77 ± 8.28 | 35.23 ± 8.48 | 35.42 ± 8.74 | 36.44 ± 10.02 | 36.10 ± 9.45 | 36.29 ± 9.94 |
| % VL-HHB | 34.82 ± 18.98 | 46.17 ± 9.29* | 62.02 ± 9.15* | 78.44 ± 12.63* | 88.11 ± 6.90* | 94.14 ± 7.50 | 94.76 ± 9.71 |
| BL GAST-HHb, µm | 19.11 ± 7.74 | 18.86 ± 7.74 | 19.19 ± 7.69 | 19.27 ± 7.80 | 20.98 ± 8.62 | 20.65 ± 8.47 | 19.82 ± 8.41 |
| % GAST-HHb | 36.18 ± 20.63 | 53.61 ± 9.44 | 63.35 ± 8.40* | 75.06 ± 9.93* | 81.60 ± 9.51 | 87.06 ± 11.05 | 98.46 ± 4.61* |

Values are mean ± SD of 9 subjects, baseline vastus lateralis deoxy-Hb (BL VL-HHb), normalized deoxy-hb vastus lateralis (% VL-HHb), baseline gastrocnemius deoxy-Hb (BL GAST-HHb), and normalized deoxy-Hb gastrocnemius (% GAST - HHb). Normalized deoxy-Hb data was calculated based on the change in HHb from baseline 30W cycling to the value obtained during the final 30 seconds of each workrate. Peak deoxy-Hb was determined for each subject and then converted to 100%. * Indicates significant increase from previous value, $p < 0.05$.

## CHAPTER VI: STUDY 3

## STROKE VOLUME RESPONSE TO LOW DOSE BETA BLOCKADE DURING NORMOTHERMIC AND HYPERTHERMIC CONDITIONS

**Abstract:**

The effect of hyperthermia on stroke volume (SV) independent of heart rate (HR) has not been described. Therefore, the purpose of this study was to determine if hyperthermia independent of an increase in HR reduces SV. Eleven active men performed 60 minutes of exercise at ~ 57% of VO2max after receiving placebo control (PL) or a low dose (0.2mg/kg) of the β1 adrenoreceptor beta blocker (βB), atenolol. Four experimental conditions were performed; normothermia and PL (NormoPL), normothermia and βB (NormoβB), hyperthermia and PL (HyperPL), and hyperthermia and βB (HyperβB). Hyperthermia increased skin and core temperature by 4.3$^{o}$C and 0.8$^{o}$C, respectively. HR at minute 60 was not different between NormoPL (154.6 ± 11.0) and HyperβB (153.8 ± 13.3 bpm) ($p > 0.05$) and SV was slightly increased during the latter portion of the exercise bout (6 to 7% increase from minute 40 to 60) during Hyper βB when compared to NormoPL (treatment x time interaction, $F = 3.234$, $p = 0.03$). The increase in SV appears to be due to the higher CO during hyperthermic conditions (minute 60: Hyper; 21.0 ± 2.5 vs. Normo 18.9 ± 2.6, $p < 0.01$). When the progressive increase in HR was not prevented by βB, SV was reduced by 9% and 14% for NormoPL and HyperPL, respectively ($p < 0.01$). Although hyperthermia increased cutaneous blood flow (CBF) and forearm blood flow (FBF) by ~40% ($p < 0.05$), these increases were not

temporally related to the decrease in SV as CBF and FBF did not increase after min 15 of exercise. In conclusion, when matched for HR, hyperthermia does not lower SV. Furthermore, the reduction in SV during exercise under both normothermic and hyperthermic conditions is due to the increase in HR.

**Introduction:**

During moderate intensity prolonged exercise, heart rate (HR) normally increases by 10 to 20 beats per minute from minute 10 to 60 of exercise. This HR drift is accompanied by a significant reduction in stroke volume (SV). Previous work from our laboratory used a low dose of beta blockade (βB) (cardioselective β1 adrenergic receptor blockade; 0.1mg/kg atenolol) to prevent the normal increase in HR which attenuated the reduction in SV without affecting thermoregulation, blood pressure, or cutaneous blood flow (CBF) (Fritzsche *et al.*, 1999). Based on the results of this study, it was believed that the increase in HR leads to a reduction in diastolic filling time which then causes the decrease in SV (Ross *et al.*, 1965; Bevegard *et al.*, 1967; Sheriff *et al.*, 1993). Furthermore, increases in CBF were shown to be temporally unrelated to the reduction in SV (Fritzsche *et al.*, 1999) which is in direct contradiction to classic studies of CV drift (Rowell, 1974, 1986) that posited a redistribution of blood volume from central to peripheral sites and a gradual and progressive increase in cutaneous blood flow caused the increase in HR and decrease in SV.

Whether or not a similar attenuation of the reduction in SV would be observed during exercise with severe heat stress has yet to be determined. During exercise in the heat the magnitude of the increase in HR is substantially greater than during moderate conditions as increased demand is placed on the cardiovascular system to deliver blood to the working muscles and to the skin to aide in thermoregulation (Shaffrath & Adams, 1984; Gonzalez-Alonso *et al.*, 2008). Under such conditions both HR and CBF are

increased leading to a substantially greater reduction in SV when compared to normal conditions (Shaffrath & Adams, 1984). The contribution that the elevation in HR and CBF independently exert on the reduction in SV is unknown.

Cardiac function appears to be reduced during exercise in the heat. Hyperthermia independent of dehydration reduced SV by 11 ml/beat; however, hyperthermia was associated with an 8 bpm higher HR (Gonzalez-Alonso *et al.*, 1997). In a follow-up study (Gonzalez-Alonso *et al.*, 1999a) supine exercise restored two thirds of the reduction in SV and prevented one third of the increase in HR. Since SV was still reduced it appeared that a factor associated with hyperthermia and not dehydration was associated with the reduction in SV.

The purpose of this study was to determine if hyperthermia, independent of an increase in HR, reduces SV. In order to answer this question a low dose of βB was used to prevent the normal increase in HR during exercise under normothermic and hyperthermic conditions. We hypothesized that hyperthermia would reduce SV when HR was matched. Furthermore, we were also able to determine if the progressive increase in HR and reduction in SV associated with exercise in the heat is temporally unrelated to peripheral hemodynamics as has been previously determined during exercise in normal environmental conditions (Fritzsche *et al.*, 1999).

**Methods:**

*Subjects:* Eleven healthy and active men (24 ± 5 yr of age; range 18 - 34) provided written informed consent to participate in this study. The protocol, experimental design, and informed consent form were approved by the Institutional Review Board at The University of Texas at Austin. The subjects' stature, body mass, peak O2 uptake (VO2peak), and maximal HR (means ± SD) were as follows: 1.767 ± 0.056 m, 77.8 ± 12.4 kg, 3.885 ± 0.541 l/min, and 192.9 ± 8.2 beats/min, respectively.

*Experimental protocol and design:*

*Preliminary testing*: The submaximal VO2 vs. workrate relationship was determined during a continuous incremental cycle ergometer protocol. Subjects rested while seated on the cycle ergometer (Excalibur Sport, Lode) for 5 minutes while VO2 and HR were monitored to determine baseline resting values. Subjects then cycled for 20 minutes (4 by 5 minutes stages) at a constant pedal rate (freely chosen by subject). Five minutes at each submaximal work rate allowed for a steady state VO2 and HR response. Following a 10 min rest, subjects returned to the cycle ergometer and VO2max and maximal HR were determined during a continuous, incremental cycle ergometer protocol.

*Familiarization trials:* Subjects performed two familiarization trials. The first familiarization trial was performed under normothermic conditions while the second was performed under hyperthermic conditions. Subjects pedaled for 60 minutes at a

constant workrate that elicited approximately 60% of VO2max. All measurements except venous blood draws were made during these familiarization trials, thereby allowing subjects to practice the acetylene wash-in (cardiac output) and venous occlusion plethysmography (forearm blood flow) techniques. During these familiarization trials subjects ingested 12 ml/kg of a 6% CHO-electrolyte beverage (Gatorade, Quaker Oats) and sweat rate was calculated for both conditions (sweat rate equal to change in nude body mass pre to post exercise minus ingested fluid volume). Fluid was ingested prior to exercise (water only) and at min 15, 30, and 45 of exercise (Gatorade).

*Experimental Trials:* Subjects cycled for 60 min at a constant work rate that elicited approximately 57% of VO2max under normothermic and hyperthermic conditions. Three minutes before the exercise bout subjects ingested: 1) 0.2 mg/kg of the β1 (cardioselective)-adrenoreceptor blocker atenolol (βB) or 2) placebo control (PLA). βB was in liquid oral suspension (2 mg/ml). One hundred milliliters of a calorie free diet cherry soda was used to mask the βB and to match the flavor of the placebo (100ml of diet cherry soda). The target amount of βB was measured using a precision scale (XP-105, Mettler-Toledo). The dosage of βB was chosen based on pilot work and previous work from our laboratory (Fritzsche *et al.*, 1999). Previously, Fritzsche et al. (Fritzsche *et al.*, 1999) gave subjects 0.1mg/kg atenolol and showed that this dosage was effective at blocking the normal increase in HR that occurs with prolonged exercise under moderate environmental conditions (dry bulb temp 27$^{o}$C, wet bulb temp 18$^{o}$C, RH

< 40%). However, based on pilot work, this dosage (0.1mg/kg) was not effective at preventing the increase in HR under hyperthermic conditions, therefore a slightly higher dosage (0.2mg/kg) was used for this study. This dosage (0.2mg/kg) resulted in a nearly identical HR response between the NormoPL and HyperβB trials (see results section). A set volume of water (specific to trial and subject) was ingested prior to exercise. A 6% CHO-electrolyte beverage (Gatorade, Quaker Oats) was ingested at min 15, 30, and 45. The total volume of water and the CHO-electrolyte beverage equaled the sweat volume as determined during the familiarization trials.

Experimental trials were performed in a random order with at least 48 hours separating the trials. Subjects were blinded as to whether or not they were performing a βB or PLA trial. All trials were performed at the same time of day to avoid any confounding effects of circadian rhythm on core temperature. Subjects were instructed to drink 500 ml of water upon waking to insure adequate hydration and to eat the same breakfast prior to each trial. Trials commenced at least 2 hours post-prandial.

*Experimental procedures:*

Upon arrival to the laboratory, subjects were escorted to a restroom adjacent to the laboratory where they voided their bladder, recorded their nude body mass, and inserted the rectal temperature probe. Subjects then dressed in cycling shorts and returned to the main laboratory to begin instrumentation. Subjects sat quietly in a chair while their skin was cleaned with 70% isopropyl alcohol for placement of ECG

electrodes. Following placement of electrodes the subjects put on a spandage shirt which held all wires and electrodes in place during exercise. An antecubital vein was catheterized for blood sampling. Following catheterization, subjects moved to the cycle ergometer and final instrumentation was performed (forearm blood flow strain gauge and laser Doppler probe placement). Resting measures of forearm blood flow (FBF), cutaneous blood flow (CBF), oxygen consumption (VO2), cardiac output (CO), and blood pressure (BP) were made prior to exercise. In order to achieve the hyperthermic conditions, subjects were dressed with a vinyl rain jacket and nylon/spandex leg coverings and two parabolic electric heaters (Heatdish, Presto) were directed at the subject, one from the front and the other from the back. The combination of the jacket, leg coverings, and heaters was successful at reducing heat dissipation as evidenced by the higher core (Tcore) and skin (Tskin) temperatures during hyperthermia trials. Normothermic conditions were achieved without fan cooling with an environmental temperature of 23$^{o}$C and 35% RH. Following instrumentation and baseline measures the subjects received their experimental treatment and started the 60 minute exercise bout.

*Respiratory and cardiovascular measurements:* Oxygen consumption was measured breath by breath using open-circuit spirometry. Subjects breathed through a two-way non rebreathing valve connected to a pneumotachometer (Hans Rudolph, Kansas City, MO). Oxygen and carbon dioxide concentration of inspired and expired gases were determined by a mass spectrometer (Perkin-Elmer MGA 1100, St. Louis, MO). Gas samples were collected at the mouthpiece via a 6-foot capillary tube

connected directly to the mass spectrometer. CO was determined by open circuit acetylene washin as described by Johnson et al. (Johnson *et al.*, 2000). Briefly, at the end of full expiration, the participants breathed for a minimum of 8 breaths through a mouthpiece connected to a bag filled with mixed gases, including 0.7% acetylene, 9.0% helium, 21% oxygen, and balance nitrogen. The concentrations of acetylene and helium were monitored by continuous sampling at the mouthpiece and data was viewed in real time on a personal computer. CO was calculated from the washin curve of the acetylene according to a single alveolar one compartment lung model. The iterative method as outlined in Johnson et al. (1999) was used for the calculation of CO. Custom software (Beck Integrated Physiological Systems) was used to determine breath by breath oxygen consumption and to calculate CO. The mass spectrometer was calibrated prior to each experimental trial using gases of known concentration. Volume was calibrated using a 3 l syringe (Hans Rudolph) at low, moderate, and high flow rates. During exercise VO2 was measured continuously from min 0 to 15, 18 to 22, 28 to 32, 38 to 42, 48 to 60. CO was measured prior to exercise and at min 5, 10, 15, 20, 30, 40, 50, and 60.

HR was measured continuously (Physioflow) and 1 minute averages were reported for the corresponding time period during which the CO measurement was made. The HR during this 1 minute average was used for the calculation of SV (SV = CO/HR). SBP and DBP were determined by auscultation on the right arm with use of a microphone under a blood pressure cuff (Tango+, Suntech). During the measurement of blood pressure the subject was instructed to relax his right arm and rest his right hand

on the handlebars of the cycle ergometer. Mean arterial pressure (MAP) was calculated as DBP + 1/3(SBP-DBP). Total peripheral resistance (TPR) was calculated during each determination of CO as TPR = MAP/CO.

*Hematocrit and hemoglobin:* Blood samples (totaling ~15 ml/treatment) were withdrawn prior to exercise and heating (hyperthermia trials) and during exercise at min 5, 15, 30, 45, and 60. The catheter was kept patent by flushing 5 ml 0.9% saline after each blood draw. Hemoglobin (Hb) concentration was analyzed in duplicate with the cyanmethemoglobin method. Hematocrit (Hct) was measured in duplicate after microcentrifugation for 15 min. The changes in blood volume and plasma volume (percent change from rest) were calculated from the changes in Hb and Hct according to the equations of Dill and Costill (Dill & Costill, 1974). Complete data for Hb and Hct is reported for 9 subjects due to technical problems with the 60 minute blood draw in 1 subject.

*Cutaneous blood flow and forearm blood flow:* Cutaneous blood flow (CBF) was measured continuously by laser-Doppler flowmetry (MoorLab, Moor Instruments Limited) on the ventral side of left forearm. Location of the laser-Doppler probe was kept consistent across trials by marking the site with an indelible marker. Forearm blood flow (FBF) was measured by venous occlusion plethysmography (EC6 plethysmograph, Hokanson) according to the procedures outlined by Whitney (Whitney, 1953). During this measurement, a flexible mercury in silastic tubing strain gauge was placed over the largest circumference of the right forearm. The placement of the gauge was kept

consistent within a trial as well as across trials by marking the location of the gauge with an indelible marker. An occlusion cuff was placed at the wrist and inflated to 250 mmHg to restrict blood flow to the hand for 2 minutes. A second cuff was placed around the upper arm and rapidly inflated to 50 mmHg which occludes venous outflow while arterial inflow continues. The increase in forearm volume, measured by the strain gauge, was plotted with data acquisition software (NIVP3, Hokanson). During the measurements the arm was suspended just above heart level in a custom made sling that was able to support the weight of the arm. In order to reduce movement artifact a member of the research team stabilized the sling. FBF was measured prior to exercise and heating and during exercise at min 12, 35, and 55. A series of at least 6 FBF measurements were performed for each time period.

*Body temperatures and rating of perceived exertion:* Rectal temperature (Tcore) was recorded using a thermistor (model 401, Measurement Specialties) inserted 12 cm past the anal sphincter. Skin temperature (Tskin) was recorded from skin thermistors (model 409A, Measurement Specialties) attached to plastic holders and placed at six skin sites; chest, back, upper arm, forearm, thigh, and calf. All skin thermistors were placed on the left side of the body and held in place with spandage and tape. Mean skin temperature was calculated based on the weighted average of the six sites (Hardy *et al.*, 1938). Body temperature was calculated based on the following equation; Tbody = (0.87*Tcore) + (0.13*Tskin) (Baum *et al.*, 1976). All temperature measurements were

made continuously and were interfaced to a PC. Rating of perceived exertion (RPE) was recorded on the 6 to 20 Borg scale (Borg, 1975) at min 5, 10, 15, 20, 30, 40, 50, and 60.

*Statistics:* A two-way (treatment x time) repeated measures ANOVA was used to determine significant differences between means. According to our original statistics plan, changes from min 10 to 60 (effect of time within a given treatment) were treated as planned comparisons and LSD comparison was used to determine significance of changes from min 10 to 60. The 60 minute values for each measurement were separately analyzed using a one-way ANOVA. If a significant main effect was found, Tukey's HSD was used to determine significant differences between means. The 60 minute comparison was chosen as this time point yielded the greatest difference between means for many of the measured variables (primarily Tcore, HR, and SV). The Sidak correction for multiple comparisons was used to determine significant differences between all other comparisons. If the sphericity assumption was violated the Greenhouse-Geisser correction was employed to ensure significant differences for the main effect. If no difference was observed between placebo and βB trials for a given temperature the trials were combined to determine the independent effect of temperature in normothermic (Normo) and hyperthermic (Hyper) conditions. Similarly, if no difference was identified between normothermia and hyperthermia within a given treatment the trials were combined to determine the independent effect of Placebo vs. Beta Blockade treatments. A paired samples t-test was used to determine significant

differences between means of combined groups. In order to determine the onset of βB a paired samples t-test was used to determine the first significant difference in HR for NormoPL vs. NormoβB and HyperPL vs. HyperβB. Significance was accepted at $p < 0.05$.

**Results:**

*Respiratory responses:* The one hour bout of exercise was performed at 147 ± 18.5 watts which elicited ~ 57% of VO2max. VO2 was similar between all trials and increased slightly from min 10 to 60 ($p < 0.01$) (Table 3.1).

*Body temperature regulation; Tcore and Tskin:* The technique employed to induce hyperthermia (combination of cycling apparel and space heaters) was successful at increasing both Tcore and Tskin during exercise (Figure 3.1 and Table 3.1). The earliest significant difference for Tcore between Normo and Hyper trials occurred at minute 30 (Normo; 37.71 ± 0.32 vs. Hyper; 37.89 ± 0.41$^{o}$C, $p < 0.01$). During exercise, Tskin was well maintained between 30.3 and 31.5$^{o}$C during Normo trials and between 35.1 and 36.0$^{o}$C during Hyper trials (Table 3.1). At minute 60, hyperthermia elevated Tcore and Tskin by 0.78$^{o}$C ($p < 0.01$) and 4.3$^{o}$C ($p < 0.01$), respectively. There were no differences for Tcore or Tskin between NormoPL and NormoβB or between the HyperPL and HyperβB trials (Figure 3.1 and Table 3.1).

*Cardiovascular responses:* The HR response under each condition is presented in Figure 3.2. During NormoPL, HR increased 11% from minute 10 to 60 (138.9 ± 13.0 to 154.6 ± 11.0 bpm, $p < 0.01$). HyperPL nearly doubled the increase in HR (i.e.; 21% increase) during this same time period (149.2 ± 11.4 to 180.1 ± 9.2 bpm, $p < 0.01$). NormoβB prevented the normal increase in HR (135.6±11.5 to 135.3 ± 12.2 bpm, $p = 0.89$). HR increased 7% during HyperBB (144.1 ±13.7 to 153.8 ± 13.3 bpm, $p < 0.01$) from

minute 10 to 60, however the last significant increase in HR during HyperβB occurred from minute 15 to 20 ($p < 0.01$) (i.e.; no significant increase in HR during HyperβB from minute 20 to 60). HR was not different at any time point when comparing NormoPL and HyperβB (Figure 3.1). Therefore, the βB treatment was successful at controlling HR despite a significant increase in Tcore and Tskin, a critical condition allowing us to directly test our hypothesis. Using the criteria as outlined in the methods section, the onset of βB occurred at minute 15 during NormoβB (141.7 vs. 136.2, $p < 0.01$) and minute 10 during HyperβB (149.2 vs. 144.1, $p = 0.03$).

The manipulation of core and skin temperature coupled with or without the βB treatment yielded a wide range in HR (Figure 3.4a). HR at minute 60 was 12% lower during NormoβB compared to NormoPL (135.3 ± 12.2 vs. 154.6 ± 11.0 bpm, $p < 0.01$) which coincided with a 13% elevation in SV (139.7 ± 21.5 vs. 123.1 ± 14.5 ml/beat, $p < 0.01$)(Figure 3.4b). HyperβB lowered HR by 17% compared to HyperPL (180.1 ± 9.2 vs. 153.8 ±13.3 bpm, $p < 0.01$) which was associated with a 16% increase in SV (132.1 ± 21.4 vs. 110.8 ± 4.3ml/beat, $p < 0.01$). SV declined over time during both NormoPL (134.9 ± 16.6 to 123.1 ± 14.5 ml/beat, $p < 0.01$) and HyperPL (128.4 ± 14.4 to 110.8 ± 14.3 ml/beat, $p < 0.01$) (Figure 3.3). HR at minute 60 was nearly identical between NormoPL and HyperβB despite significantly different Tcore and Tskin. Contrary to our original hypothesis that hyperthermia, independent of HR, would reduce SV, hyperthermia increased SV as evidenced by the 6 to 7% higher SV when comparing HyperβB and NormoPL at minute 40, 50, and 60 (treatment x time interaction; $F = 3.234$, $p <0.03$)

(Figure 3.5). The elevation in SV during HyperβB is most likely due to the 6% increase in CO ($p < 0.01$) (Figure 3.4c) as a result of increased cutaneous blood flow during hyperthermic conditions (Table 3.1). Based on these findings, the increase in HR appears responsible for the reduction in SV observed under both normothermic and hyperthermic conditions (Figure 3.5).

*Blood Pressure and Total Peripheral Resistance:* Hyperthermia, under both PLA and βB, lowered MAP and DBP during exercise (Table 3.1 and Figure 3.4d). At minute 60, MAP and DBP were 7% ($p < 0.01$) and 18% ($p < 0.01$) lower during Hyper than Normo trials, respectively (Figure 3.4d). Unlike MAP and DBP, βB, independent of temperature, reduced SBP during the final 20 minutes of exercise. At minute 60, βB reduced SBP by 5% ($p < 0.01$). Due to the reduction in MAP, hyperthermia reduced TPR throughout exercise compared to normothermia ($p < 0.01$).

*FBF and CBF:* FBF and CBF were not different between the two normothermia trials or between the two hyperthermia trials. Hyperthermia alone increased FBF and CBF at minute 60 FBF by 40% ($p < 0.01$) and 37% ($p < 0.01$), respectively (Table 3.1). Both FBF and CBF did not increase significantly after minute 15.

*Bodyweight changes, fluid intake, and sweat volume:* Fluid replacement maintained bodyweight (BW) between + 0.1kg and - 0.2kg of pre-exercise BW (Table 3.2). The change in BW from pre to post exercise was significant for NormoβB ($p = 0.04$), HyperPL ($p < 0.05$), and HyperβB ($p = 0.01$); however, such minor changes in BW are

assumed to not be physiologically important. Moreover, there were no differences in pre or post exercise BW between any of the treatments. Hyperthermia, on average, increased total sweat volume by 0.58 L ($p < 0.01$). In order to compensate for this increased sweat volume subjects ingested approximately 0.35 L more fluid during the hyperthermia trials (Table 3.2).

*Blood volume and plasma volume:* BV and PV were reduced during exercise compared to rest for all trials. The reductions in both BV and PV were maintained throughout exercise and there were no differences between trials indicating that the observed differences in SV were not due to differences in BV and PV. At min 60 BV and PV were reduced by 5.7% (range: 4.2 to 6.7%) and 8.4% (range: 6.5 to 10.6%), respectively (Table 3.3).

*Perceived exertion:* There were no significant differences in RPE between NormoPL and NormoβB or between HyperPL and HyperβB. The first indication that the hyperthermia trials were perceived as being more difficult occurred at minute 30, coinciding with the first significant difference in Tcore between the Hyper and Normo trials. At min 60 RPE was 1.7 points higher during Hyper than Normo (14.1 ± 1.2 vs. 15.8 ± 1.7, $p < 0.01$) (Table 3.1).

**Discussion:**

We sought to determine whether hyperthermia, independent of elevations in HR, would reduce SV. Contrary to our original hypothesis, whole body hyperthermia did not lower SV when the increase in HR was prevented (i.e.; NormoPL vs. HyperBB). Hyperthermia had no independent effect on reducing SV. However, under normal conditions when HR is allowed to increase SV is reduced (NormoPL and HyperPL). As a result of increased peripheral blood flow (CBF and FBF) CO was slightly elevated during hyperthermia. With nearly identical heart rates between these two conditions, hyperthermia elevated SV by 6 to 7% during HyperβB when compared to NormoPL (significant treatment x time interaction, $p < 0.03$). Based upon the findings of this study it appears that there is a wide range in which HR can influence SV and that the reduction in SV during both normothermia and hyperthermia is due to the elevation in HR.

The finding that hyperthermia, independent of the increase in HR, did not lower SV during moderate intensity exercise was surprising. The hypothesis for this investigation was based on findings of reduced cardiac function during intense or prolonged exercise in the heat (Gonzalez-Alonso *et al.*, 1995; Gonzalez-Alonso *et al.*, 1997; Gonzalez-Alonso *et al.*, 1998; Gonzalez-Alonso *et al.*, 1999a; Gonzalez-Alonso *et al.*, 1999b; Gonzalez-Alonso *et al.*, 2000; Gonzalez-Alonso & Calbet, 2003; Gonzalez-Alonso *et al.*, 2004; Mortensen *et al.*, 2005; Gonzalez-Alonso *et al.*, 2008). Hyperthermia, independent of dehydration, reduced SV by 11 ml/beat; however, hyperthermia was associated with an 8 bpm higher HR (Gonzalez-Alonso *et al.*, 1997). In

a follow-up study (Gonzalez-Alonso *et al.*, 1999a) supine exercise restored two thirds of the reduction in SV and prevented one third of the increase in HR. Since SV was still reduced it appeared that a factor associated with hyperthermia and not dehydration was associated with the reduction in SV. Based on the findings of these studies, hyperthermia appears to be a critical factor affecting cardiac function during prolonged exercise. An important difference between the present study and those previously discussed by Gonzalez-Alonso et al. is that the degree of hyperthermia was substantially less in the current study (38.9$^{o}$C vs. 39.5 to 40$^{o}$C). The higher core temperature may be critical to induce a reduction in SV during prolonged exercise. However, such a high core temperature is difficult to attain at a moderate exercise intensities without dehydration or without an uncompensable heat stress.

Similarly, heat stress during maximal exercise results in an acceleration of the decline in CO and MAP that leads to a reduction in muscle blood flow, O2 delivery, and O2 uptake (Gonzalez-Alonso *et al.*, 1999b; Gonzalez-Alonso & Calbet, 2003; Gonzalez-Alonso *et al.*, 2004). In fact, figure 5 of Gonzalez-Alonso et al. (Gonzalez-Alonso & Calbet, 2003) shows a leftward shift in SV when comparing heat stress to normal conditions indicative of reduced cardiac function during exercise. Similarly, maximal values of CO, SV, systemic O2 delivery and VO2 were attained within 5 minutes of exercise at VO2max and were reduced prior to exhaustion which coincided with a high core temperature (~ 39.5$^{o}$ C) (Mortensen *et al.*, 2005). Based upon these findings and the strong association between elevated Tcore and reduced cardiac function we

hypothesized that hyperthermia, independent of increases in HR, would lower SV. However, the cardiovascular adjustments to heat stress during moderate intensity exercise, as performed in this study, appear to be more similar to passive heat stress at rest than during maximal exercise. During maximal exercise, cardiac function is maximal (i.e.; VO2, HR, CO are all at maximum) and any increase in the demand for the limited CO will lead to an accelerated rate of fatigue (Gonzalez-Alonso *et al.*, 1999b; Gonzalez-Alonso *et al.*, 2004; Gonzalez-Alonso *et al.*, 2008).

Passive heat stress at rest can induce significant cardiovascular strain by increasing HR well above 100 bpm and can increase CO up to 13 l/min (Crandall, 2008; Crandall *et al.*, 2008). An elevation of 1$^{o}$C at rest was found to increase ejection fraction by lowering ESV while EDV was maintained (Crandall, 2008; Crandall *et al.*, 2008). This finding, along with prior reports of sustained or elevated stroke volume during heat stress (Rowell *et al.*, 1969; Rowell, 1986; Johnson & DW, 1996; Wilson *et al.*, 2007), coupled with reduction in cardiac filling pressure (Rowell *et al.*, 1969; Minson *et al.*, 1998; Crandall *et al.*, 1999; Peters *et al.*, 2000; Wilson *et al.*, 2007), indicate that heat stress increases cardiac contractility. Furthermore, Crandall et al. (Crandall *et al.*, 2008) found that despite a reduction in central venous and left ventricular filling pressure during passive heat stress, left ventricular EDV was unchanged by heat stress and that the heat stress may improve diastolic function resulting in greater diastolic filling for a given filling pressure. This improved diastolic function during heat stress may be related to a shift in the operating point to a steeper portion of the Frank-Starling curve where

small changes in pulmonary capillary wedge pressure (estimated left ventricular filling pressure) result in large changes in SV (Wilson *et al.*, 2009). Although invasive measures of cardiac function were not made during the present study, this is the first time that heat stress in combination with moderate intensity exercise has been shown to maintain and increase SV for a given HR under hyperthermic conditions (i.e.; HyperβB vs. NormoPL comparison).

Previous work from our laboratory (Fritzsche *et al.*, 1999) showed that during prolonged exercise the reduction in SV corresponds to the increase in HR and is temporally unrelated to an increase in cutaneous blood flow. The findings of the current study confirm these earlier results and for the first time, provide further evidence that HR is the primary factor determining SV even under conditions of hyperthermia. This finding is in direct opposition to the hypothesis put forth by Rowell that cardiovascular drift is the consequence of a progressive increase in cutaneous blood flow (Rowell, 1974, 1986). The classic thinking regarding CV drift (Rowell, 1986) is that a rise in cutaneous blood flow leads to an increase in skin venous volume, which reduces ventricular filling pressure, end diastolic volume, and SV. However, even under the hyperthermic conditions present in the current study in which FBF and CBF were elevated by 40%, blocking the normal increase in HR prevented the drop in SV. Therefore, an alternative hypothesis that the decline in SV during prolonged exercise is caused by a reduction in ventricular filling time leading to a reduction in end diastolic volume as a result of the increased HR (Ross *et al.*, 1965; Bevegard *et al.*, 1967; Sheriff *et*

*al.*, 1993) appears to be appropriate under both normothermic and hyperthermic conditions.

The mechanism responsible for the reduction in SV during prolonged exercise appears to be associated with a reduction in diastolic filling time which leads to a decrease in EDV and SV. As with the previous study from our laboratory (Fritzsche *et al.*, 1999), it appears unlikely that an unknown mechanism related to the presence of the βB prevented the decline in SV. Furthermore, some variables that could have been causally related to the decline in SV (blood volume, CBF, FBF, Tskin, and Tcore) were not different between NormoPL and NormoβB or between HyperPL and HyperβB. CBF, FBF, Tcore, and Tskin were all higher during hyperthermic conditions and these increases are most likely responsible for the greater increase in HR reduction in SV during HyperPL when compared to NormoPL. However, these increases in peripheral blood flow are not temporally associated with the drift in HR and reduction in SV as neither CBF nor FBF increased from min 15 to 60 of exercise. Under the hyperthermic conditions employed in the current study the cardiovascular system was able to respond appropriately to the increase in thermoregulatory demand by increasing skin blood flow and CO. A similar increase in CO (1 to 3 l/min) has been reported during low intensity cycling in the heat (Savard *et al.*, 1988; Nielsen *et al.*, 1990; Nielsen *et al.*, 1993). However, if such conditions are prolonged (> 90 minutes) or accompanied by significant dehydration, the cardiovascular system may not be able to meet the demands of the thermoregulatory

system as CO and MAP are reduced and progressive increases in core temperature will lead to fatigue (Gonzalez-Alonso *et al.*, 1999b).

The reason for the increase in HR during the 10 to 60 min period of prolonged exercise is not entirely clear. Based on the results of this study and Fritzsche et al. (Fritzsche *et al.*, 1999) the progressive increase in HR during both normothermic and hyperthermic conditions is not temporally related to progressive increases in CBF, FBF, or Tskin as these variables did not change from min 10 or 15 to 60 of exercise. Typically during prolonged exercise when the HR increase is prevented by reducing the environmental stress, reducing the exercise intensity (Shaffrath & Adams, 1984), or by having well trained, euhydrated, heat acclimated athletes (Gonzalez-Alonso *et al.*, 1995; Gonzalez-Alonso *et al.*, 1997) perform the exercise bout the increases in perceived exertion and core temperature are also prevented. However, due to the pharmacological intervention in the present study, increases in RPE and Tcore were disassociated from HR during the βB trials. An alternate explanation for the increase in HR as put forth by Fritzsche et al. (Fritzsche *et al.*, 1999) is that a progressive increase in motor unit recruitment coupled with a minor increase in core temperature may account for the increase in HR. The current findings from the hyperthermia and the normothermia trials lend support for the role of the progressive increase in Tcore leading to the increase in HR. During normothermia, a 0.9$^{o}$C increase in Tcore was associated with a 16 bpm increase in HR and during hyperthermia a 1.7$^{o}$C increase in Tcore was associated with a 30 bpm increase in HR. Furthermore, VO2 increased 6.5%

over the duration of the exercise bout (present study and Fritzsche *et al.*, 1999) which may be related to a progressive increase in motor unit recruitment.

Overall, hyperthermia independent of an increase in HR was not associated with a reduction in SV. Due to the elevation in CO associated with an increase in skin blood flow during hyperthermia, SV was slightly elevated when the increase in HR was prevented (HyperβB vs. NormoPL). The increase in HR that occurs during normal exercise appears to be the primary factor responsible for the decrease in SV under both normothermic and hyperthermic conditions. The progressive increase in HR, although not entirely understood, appears to be associated with the progressive increase in core temperature as other factors such as cutaneous blood flow and skin temperature are not temporally related to the increase in HR during exercise under both normothermic and hyperthermic conditions.

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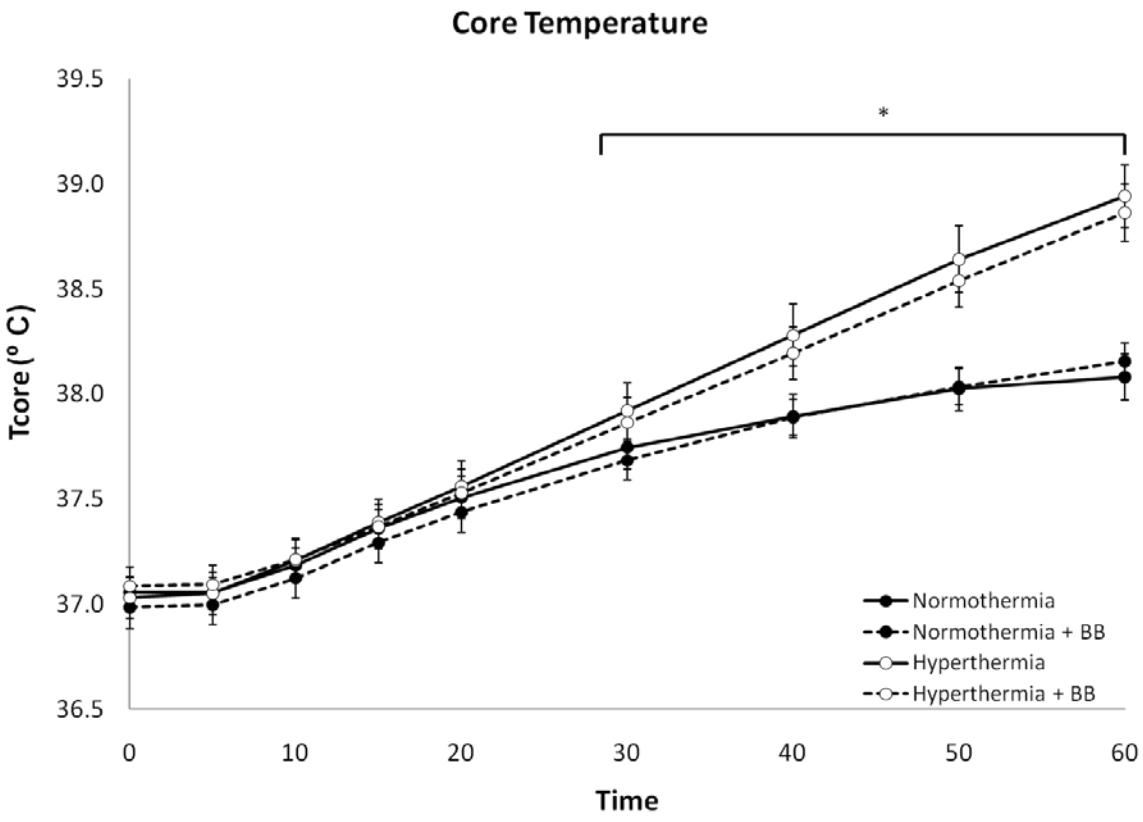



Figure 3.1: Values are mean ± SE of 11 subjects. * Indicates significant difference between pooled data for normothermia and hyperthermia trials, $p < 0.05$.

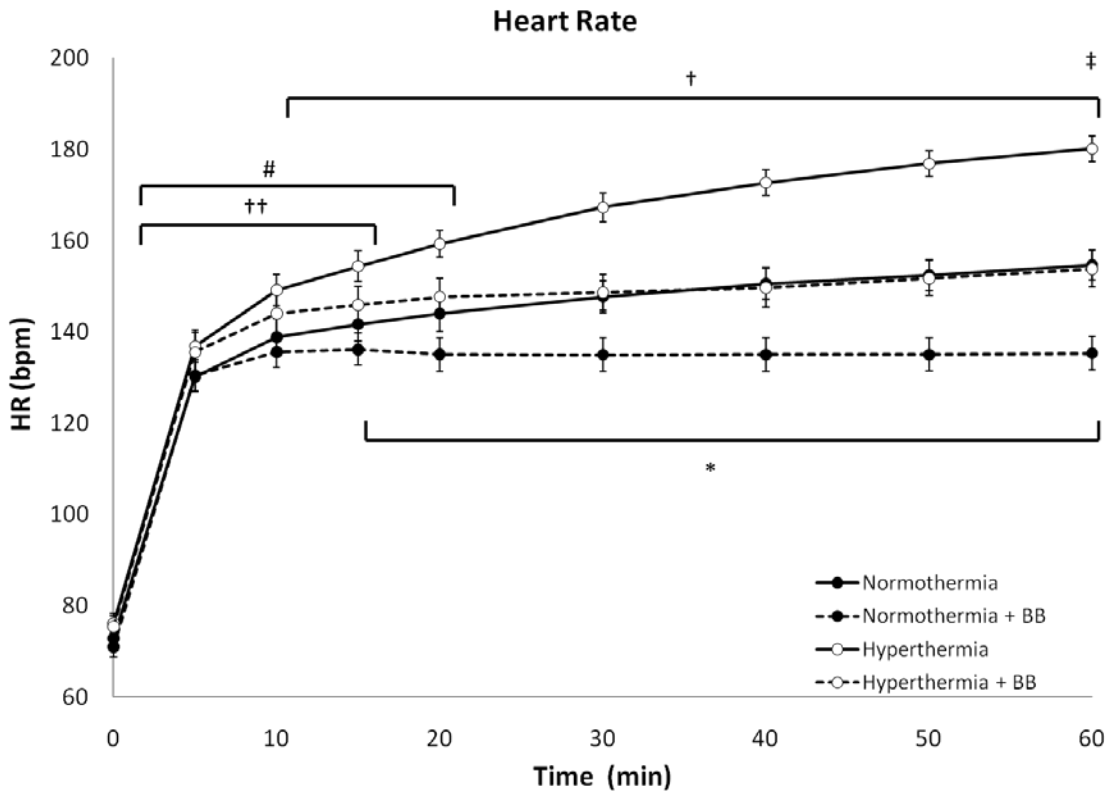



Figure 3.2: Values are mean ± SE for 11 subjects. * Indicates significant difference between NormoPL and NormoβB, † indicates significant difference between HyperPL and HyperβB, # indicates significant increase from previous value for HyperβB, †† indicates significant increase from previous value for NormoPL. Both HyperPL and NormoPL exhibited a continual significant increase in HR, however for the purpose of clarity this is not included on the above graph. ‡ Indicates significant increase from min 10 for NormoPL, HyperPL and HyperβB, $p < 0.05$.

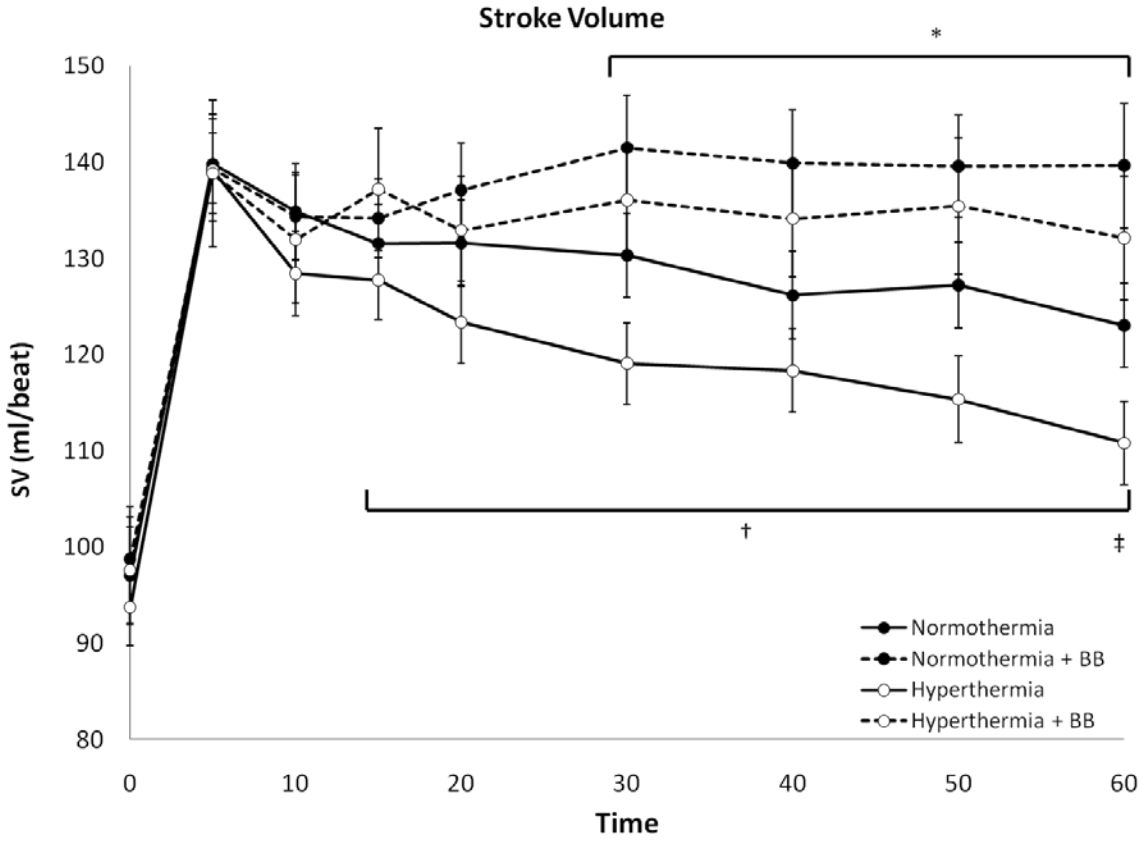



Figure 3.3: Values are mean ± SE for 11 subjects. * Indicates significant difference between NormoPL and NormoβB, † indicates significant difference between HyperPL and HyperβB. ‡ indicates significant decrease from min 10 for NormoPL and HyperPL, $p < 0.05$.

Figure 3.4A

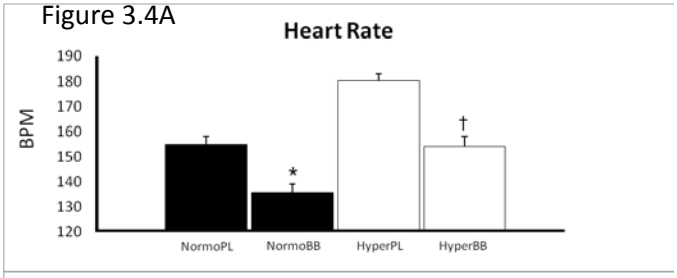
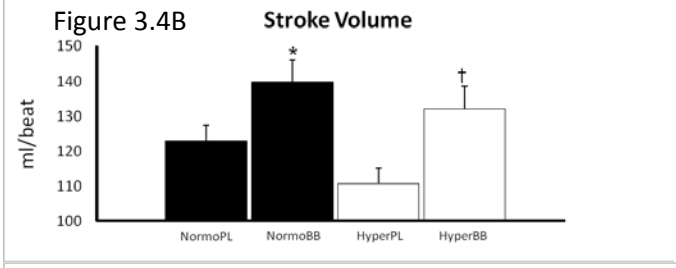



Figure 3.4B

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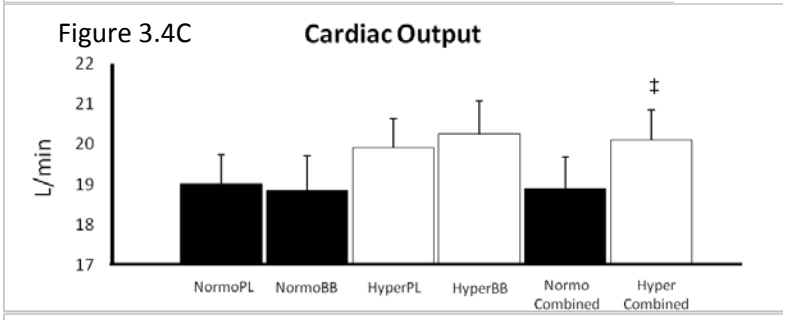


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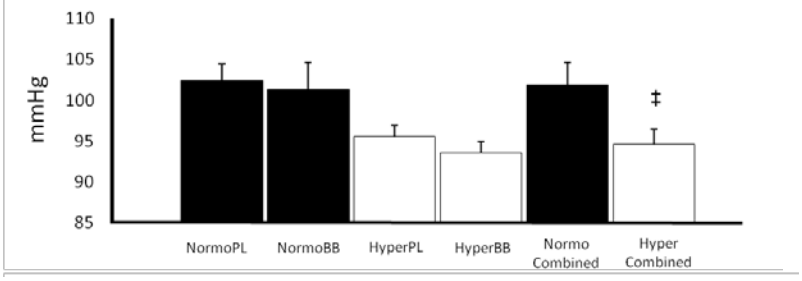


Figure 3.4E

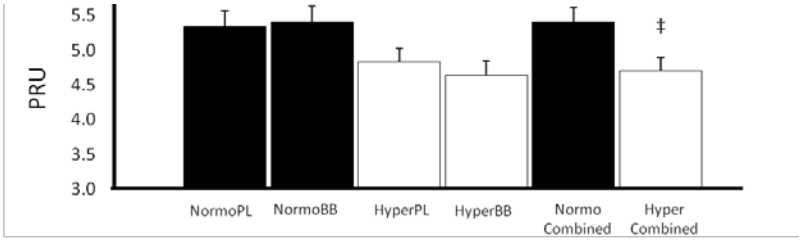

Figure 3.4A-E: Values are mean ± SE of 11 subjects. All graphs depict values at min 60 of exercise ; A) heart rate, B) stroke volume, C) cardiac output, D) mean arterial blood pressure, and E) total peripheral resistance. * Indicates significant difference between NormoPL and NormoβB, † indicates significant difference between HyperPL and HyperβB, ‡ indicates significant difference between pooled data from Normo and Hyper showing independent effect of temperature, $p < 0.05$.

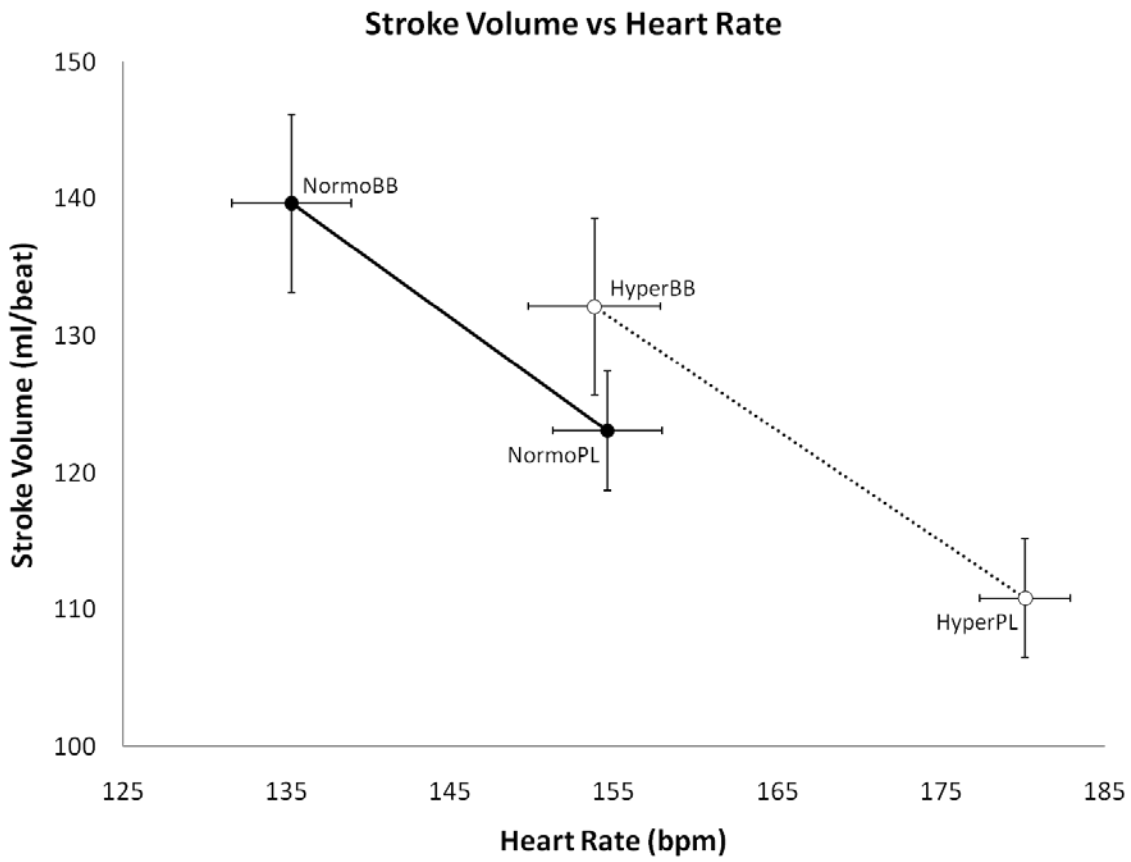


Figure 3.5: Values are mean ± SD of 11 subjects. Normothermia conditions are represented by the solid line and filled circles (•). Hyperthermia conditions are represented by the dotted line and open circles (o). Hyperthermia resulted in a rightward shift of the SV vs. HR curve. Significant treatment by time interaction for SV for NormoPL vs HyperβB comparison ($F = 3.234$, $p = 0.03$).

Table 3.1: *Exercise responses during 1 hour exercise bout under normothermia + PL (NormoPL), normothermia + BB (NormoBB), hyperthermia + PL (HyperPL), and hyperthermia + BB (HyperBB) conditions*

| TIME, min | Rest | 5 | 10 | 15 | 20 | 30 | 40 | 50 | 60 |
|---|---|---|---|---|---|---|---|---|---|
| VO2, l/min | | | | | | | | | |
| NormoPL | 0.364 ± 0.099 | 2.120 ± 0.298 | 2.186 ± 0.280 | 2.198 ± 0.296 | 2.254 ± 0.321 | 2.254 ± 0.318 | 2.272 ± 0.323 | 2.286 ± 0.312 | 2.289 ± 0.319† |
| NormoBB | 0.365 ± 0.149 | 2.102 ± 0.259 | 2.123 ± 0.271 | 2.153 ± 0.294 | 2.207 ± 0.280 | 2.230 ± 0.335 | 2.252 ± 0.316 | 2.279 ± 0.312 | 2.242 ± 0.342† |
| HyperPL | 0.350 ± 0.170 | 2.069 ± 0.283 | 2.134 ± 0.322 | 2.145 ± 0.318 | 2.241 ± 0.327 | 2.255 ± 0.336 | 2.257 ± 0.387 | 2.292 ± 0.358 | 2.302 ± 0.378† |
| HyperBB | 0.318 ± 0.114 | 2.040 ± 0.280 | 2.080 ± 0.290 | 2.126 ± 0.291 | 2.197 ± 0.324 | 2.199 ± 0.354 | 2.211 ± 0.314 | 2.243 ± 0.331 | 2.257 ± 0.340† |
| CO, l/min | | | | | | | | | |
| NormoPL | 7.0 ± 1.1 | 18.1 ± 2.2 | 18.6 ± 1.9 | 18.6 ± 2.1 | 18.9 ± 2.3 | 19.2 ± 2.2 | 18.9 ± 2.2 | 19.3 ± 2.1 | 19.0 ± 2.4 |
| NormoBB | 6.9 ± 1.1 | 18.1 ± 1.7 | 18.1 ± 1.9 | 18.2 ± 1.7 | 18.4 ± 2.1 | 19.1 ± 2.6 | 18.8 ± 2.4 | 18.8 ± 2.3 | 18.8 ± 2.9 |
| ***NORMO*** | ***7.0 ± 1.1*** | ***18.1 ± 1.9*** | ***18.4 ± 1.9*** | ***18.4 ± 1.9*** | ***18.7 ± 2.1*** | ***19.1 ± 2.4*** | ***18.9 ± 2.2*** | ***19.1 ± 2.2*** | ***18.9 ± 2.6*** |
| HyperPL | 7.1 ± 0.9 | 19.0 ± 2.3 | 19.1 ± 2.0 | 19.6 ± 1.8 | 19.6 ± 1.9 | 19.9 ± 2.2 | 20.4 ± 2.4 | 20.4 ± 2.5 | 19.9 ± 2.4 |
| HyperBB | 7.3 ± 1.0 | 18.8 ± 2.7 | 19.0 ± 2.6 | 20.0 ± 2.4 | 19.6 ± 2.5 | 20.1 ± 2.6 | 19.9 ± 2.2 | 20.5 ± 2.8 | 20.3 ± 2.8 |
| ***HYPER*** | ***7.2 ± 0.9*** | ***18.9 ± 2.4**** | ***19.1 ± 2.3**** | ***19.8 ± 2.1**** | ***19.6 ± 2.2**** | ***20.0 ± 2.4**** | ***20.2 ± 2.2**** | ***20.4 ± 2.6**** | ***20.1 ± 2.5*†*** |
| SBP, mmHg | | | | | | | | | |
| NormoPL | 126.7 ± 8.1 | 168.9 ± 9.3 | 179.9 ± 15.3 | 184.0 ± 13.9 | 182.7 ± 14.9 | 182.5 ± 14.7 | 183.1 ± 16.3 | 183.0 ± 12.2 | 181.5 ± 15.6 |
| NormoBB | 127.5 ± 11.9 | 170.5 ± 13.6 | 181.3 ± 21.7 | 184.2 ± 20.1 | 182.0 ± 18.1 | 176.9 ± 18.8 | 172.5 ± 17.6 | 172.4 ± 14.8 | 169.2 ± 14.0 |
| HyperPL | 128.9 ± 9.5 | 170.8 ± 14.4 | 179.5 ± 17.4 | 182.9 ± 19.8 | 184.6 ± 14.9 | 184.6 ± 16.5 | 185.3 ± 20.0 | 179.6 ± 12.9 | 180.3 ± 14.0 |
| HyperBB | 127.6 ± 9.2 | 167.3 ± 10.7 | 177.6 ± 17.7 | 177.4 ± 14.9 | 181.5 ± 16.4 | 179.9 ± 20.7 | 176.0 ± 16.8 | 175.3 ± 16.7 | 173.3 ± 15.6 |
| ***PLACEBO*** | ***127.8 ± 8.8*** | ***169.9 ± 11.9*** | ***179.7 ± 16.4*** | ***183.4 ± 16.8*** | ***183.7 ± 14.9*** | ***183.5 ± 15.6*** | ***184.2 ± 18.1*** | ***181.3 ± 12.6*** | ***180.9 ± 14.8*** |
| ***BB*** | ***127.5 ± 10.5*** | ***168.9 ± 12.1*** | ***179.5 ± 19.7*** | ***180.8 ± 17.5*** | ***181.8 ± 17.3*** | ***178.4 ± 19.7**** | ***174.2 ± 17.2**** | ***173.8 ± 15.7**** | ***171.2 ± 14.8*†*** |
| DBP, mmHg | | | | | | | | | |
| NormoPL | 77.2 ± 10.4 | 77.5 ± 10.1 | 73.9 ± 10.1 | 68.0 ± 5.4 | 69.6 ± 7.6 | 66.8 ± 10.8 | 66.7 ± 8.7 | 69.2 ± 7.4 | 62.9 ± 7.6 |
| NormoBB | 81.9 ± 6.8 | 80.6 ± 9.7 | 79.8 ± 10.7 | 77.8 ± 10.8 | 73.0 ± 10.1 | 72.1 ± 13.0 | 69.9 ± 13.1 | 69.9 ± 11.9 | 67.0 ± 14.2 |
| ***NORMO*** | ***79.5 ± 8.6*** | ***79.0 ± 9.9*** | ***76.8 ± 10.4*** | ***72.9 ± 8.1*** | ***71.3 ± 8.9*** | ***69.5 ± 11.9*** | ***68.3 ± 10.9*** | ***69.5 ± 9.7*** | ***65.0 ± 10.9*†*** |
| HyperPL | 77.9 ± 3.8 | 70.7 ± 9.3 | 67.2 ± 11.8 | 62.2 ± 11.3 | 64.0 ± 10.8 | 60.0 ± 10.5 | 53.3 ± 8.5 | 54.0 ± 6.2 | 53.2 ± 6.7 |
| HyperBB | 77.4 ± 6.6 | 69.0 ± 9.7 | 65.8 ± 9.2 | 65.1 ± 8.0 | 63.7 ± 9.1 | 60.2 ± 13.7 | 59.0 ± 14.2 | 55.5 ± 10.3 | 53.8 ± 10.5 |
| ***HYPER*** | ***77.7 ± 5.2*** | ***69.9 ± 9.5**** | ***66.5 ± 10.5**** | ***63.6 ± 9.7**** | ***63.9 ± 10.0**** | ***60.1 ± 12.1**** | ***56.1 ± 11.3**** | ***54.7 ± 8.3**** | ***53.5 ± 8.6*†*** |
| MAP, mmHg | | | | | | | | | |
| NormoPL | 93.7 ± 8.5 | 107.9 ± 7.8 | 109.2 ± 5.4 | 107.0 ± 4.4 | 107.3 ± 6.0 | 105.4 ± 9.1 | 105.5 ± 5.6 | 107.1 ± 5.1 | 102.4 ± 6.9 |
| NormoBB | 96.0 ± 6.8 | 110.6 ± 7.5 | 113.2 ± 9.7 | 112.5 ± 10.0 | 109.6 ± 9.3 | 107.0 ± 10.7 | 104.2 ± 10.9 | 104.6 ± 8.0 | 101.3 ± 11.1 |
| ***NORMO*** | ***94.9 ± 7.7*** | ***109.3 ± 7.7*** | ***111.2 ± 7.6*** | ***109.7 ± 7.2*** | ***108.4 ± 7.7*** | ***106.2 ± 9.9*** | ***104.8 ± 8.3*** | ***105.9 ± 6.6*** | ***101.9 ± 9.0†*** |
| HyperPL | 94.9 ± 4.1 | 104.1 ± 5.3 | 104.6 ± 8.9 | 102.4 ± 7.8 | 104.2 ± 6.7 | 101.5 ± 8.1 | 97.3 ± 6.8 | 95.9 ± 5.1 | 95.6 ± 4.4 |
| HyperBB | 94.1 ± 6.4 | 101.8 ± 7.6 | 103.1 ± 7.6 | 102.5 ± 5.6 | 102.9 ± 6.4 | 100.1 ± 9.0 | 98.0 ± 7.0 | 95.4 ± 6.0 | 93.6 ± 7.7 |
| ***HYPER*** | ***94.5 ± 5.3*** | ***102.9 ± 6.5**** | ***103.9 ± 8.2**** | ***102.5 ± 6.7**** | ***103.6 ± 6.6**** | ***100.8 ± 8.5**** | ***97.6 ± 6.9**** | ***95.6 ± 5.6**** | ***94.6 ± 6.1*†*** |

Table 3.1 (continued): *Exercise responses during 1 hour exercise bout under normothermia + PL (NormoPL), normothermia + BB (NormoBB), hyperthermia + PL (HyperPL), and hyperthermia + BB (HyperBB) conditions*

| TIME, min | Rest | 5 | 10 | 15 | 20 | 30 | 40 | 50 | 60 |
|---|---|---|---|---|---|---|---|---|---|
| TPR, pru | | | | | | | | | |
| NormoPL | 13.58 ± 2.02 | 6.07 ± 0.82 | 5.96 ± 0.88 | 5.70 ± 0.74 | 5.74 ± 0.74 | 5.50 ± 0.85 | 5.48 ± 0.66 | 5.61 ± 0.58 | 5.34 ± 0.73 |
| NormoBB | 14.22 ± 2.03 | 6.10 ± 0.69 | 6.18 ± 0.87 | 6.10 ± 0.64 | 5.96 ± 0.70 | 5.64 ± 0.64 | 5.50 ± 0.78 | 5.58 ± 0.74 | 5.41 ± 0.75 |
| ***NORMO*** | ***13.90 ± 2.03*** | ***6.09 ± 0.76*** | ***6.07 ± 0.88*** | ***5.90 ± 0.69*** | ***5.85 ± 0.72*** | ***5.57 ± 0.74*** | ***5.49 ± 0.72*** | ***5.60 ± 0.66*** | ***5.37 ± 0.74†*** |
| HyperPL | 13.58 ± 1.44 | 5.60 ± 0.68 | 5.55 ± 0.60 | 5.27 ± 0.51 | 5.33 ± 0.63 | 5.08 ± 0.50 | 4.87 ± 0.58 | 4.85 ± 0.62 | 4.83 ± 0.63 |
| HyperBB | 13.11 ± 1.61 | 5.46 ± 0.97 | 5.47 ± 0.80 | 5.18 ± 0.72 | 5.37 ± 0.90 | 4.98 ± 0.82 | 4.96 ± 0.77 | 4.73 ± 0.64 | 4.64 ± 0.69 |
| ***HYPER*** | ***13.34 ± 1.52*** | ***5.53 ± 0.82**** | ***5.51 ± 0.70**** | ***5.22 ± 0.61**** | ***5.35 ± 0.76**** | ***5.03 ± 0.66**** | ***4.91 ± 0.68**** | ***4.79 ± 0.63**** | ***4.74 ± 0.66*†*** |
| Tskin, $^{o}$C | | | | | | | | | |
| NormoPL | 30.80 ± 0.68 | 30.45 ± 0.67 | 30.85 ± 0.77 | 31.49 ± 0.52 | 31.52 ± 0.47 | 31.61 ± 0.49 | 31.57 ± 0.56 | 31.31 ± 0.69 | 31.47 ± 0.71 |
| NormoBB | 30.60 ± 0.46 | 30.27 ± 0.45 | 30.65 ± 0.53 | 31.25 ± 0.35 | 31.24 ± 0.24 | 31.37 ± 0.26 | 31.28 ± 0.42 | 31.10 ± 0.46 | 31.32 ± 0.60 |
| ***NORMO*** | ***30.70 ± 0.58*** | ***30.36 ± 0.56*** | ***30.75 ± 0.65*** | ***31.37 ± 0.45*** | ***31.38 ± 0.39*** | ***31.49 ± 0.40*** | ***31.43 ± 0.51*** | ***31.21 ± 0.58*** | ***31.40 ± 0.65*** |
| HyperPL | 34.83 ± 0.69 | 35.13 ± 0.84 | 35.68 ± 0.93 | 35.70 ± 0.75 | 35.80 ± 0.55 | 35.82 ± 0.60 | 35.99 ± 0.68 | 35.91 ± 0.74 | 35.91 ± 0.71 |
| HyperBB | 35.02 ± 0.91 | 35.14 ± 1.01 | 35.60 ± 1.02 | 35.59 ± 0.80 | 35.61 ± 0.74 | 35.55 ± 0.78 | 35.63 ± 0.87 | 35.43 ± 0.80 | 35.51 ± 0.78 |
| ***HYPER*** | ***34.93 ± 0.79**** | ***35.14 ± 0.91**** | ***35.64 ± 0.95**** | ***35.64 ± 0.76**** | ***35.70 ± 0.64**** | ***35.68 ± 0.70**** | ***35.81 ± 0.79**** | ***35.67 ± 0.79**** | ***35.71 ± 0.75**** |
| FBF, ml/100ml/min | | | | | | | | | |
| NormoPL | 1.70 ± 0.75 | | 8.06 ± 3.27 | | | 9.31 ± 3.48 | | | 9.65 ± 3.87 |
| NormoBB | 1.92 ± 0.94 | | 9.13 ± 3.20 | | | 10.33 ± 2.74 | | | 11.68 ± 4.26 |
| ***NORMO*** | ***1.81 ± 0.84*** | | ***8.59 ± 3.20*** | | | ***9.82 ± 3.10*** | | | ***10.67 ± 4.10*** |
| HyperPL | 2.06 ± 1.04 | | 14.33 ± 4.39 | | | 16.76 ± 5.19 | | | 15.39 ± 4.67 |
| HyperBB | 2.20 ± 1.19 | | 14.48 ± 4.46 | | | 15.75 ± 3.91 | | | 14.48 ± 4.45 |
| ***HYPER*** | ***2.13 ± 1.09*** | | ***14.40 ± 4.32**** | | | ***16.26 ± 4.52**** | | | ***14.94 ± 4.48**** |
| CBF, arbitray units | | | | | | | | | |
| NormoPL | 26.2 ± 7.9 | 41.4 ± 14.4 | 84.1 ± 43.5 | 103.4 ± 31.8 | 101.0 ± 34.0 | 112.9 ± 46.7 | 118.1 ± 46.9 | 115.4 ± 45.1 | 115.8 ± 41.1 |
| NormoBB | 24.7 ± 6.4 | 37.6 ± 15.2 | 89.0 ± 43.4 | 100.4 ± 39.0 | 104.5 ± 39.8 | 104.7 ± 35.0 | 107.1 ± 34.3 | 108.8 ± 31.5 | 106.5 ± 29.0 |
| ***NORMO*** | ***25.4 ± 7.0*** | ***39.5 ± 14.6*** | ***86.6 ± 42.4*** | ***101.9 ± 34.7*** | ***102.7 ± 36.1*** | ***108.8 ± 40.4*** | ***112.6 ± 40.4*** | ***112.1 ± 38.0*** | ***111.1 ± 35.0†*** |
| HyperPL | 34.6 ± 12.0 | 90.9 ± 56.2 | 147.4 ± 73.4 | 147.7 ± 67.2 | 151.3 ± 55.3 | 159.6 ± 72.1 | 160.4 ± 67.3 | 142.2 ± 43.7 | 145.0 ± 43.6 |
| HyperBB | 56.5 ± 83.5 | 109.3 ± 97.8 | 145.8 ± 80.5 | 145.5 ± 68.1 | 163.2 ± 71.8 | 139.4 ± 71.3 | 156.0 ± 56.2 | 151.0 ± 45.4 | 158.8 ± 45.6 |
| ***HYPER*** | ***45.6 ± 59.1*** | ***100.1 ± 78.2**** | ***146.6 ± 75.0**** | ***146.6 ± 65.8**** | ***157.3 ± 62.7**** | ***149.5 ± 70.5**** | ***158.2 ± 60.4**** | ***146.6 ± 43.6**** | ***151.9 ± 44.0**** |
| RPE | | | | | | | | | |
| NormoPL | | 11.6 ± 1.3 | 12.1 ± 1.1 | 12.5 ± 0.8 | 12.5 ± 0.8 | 12.9 ± 0.8 | 13.0 ± 0.8 | 13.3 ± 1.1 | 13.8 ± 1.0 |
| NormoBB | | 12.0 ± 1.4 | 12.2 ± 1.2 | 12.5 ± 0.8 | 13.1 ± 0.9 | 13.0 ± 0.8 | 13.5 ± 1.1 | 13.9 ± 0.8 | 14.4 ± 1.3 |
| ***NORMO*** | | ***11.8 ± 1.3*** | ***12.1 ± 1.1*** | ***12.5 ± 0.8*** | ***12.8 ± 0.9*** | ***12.9 ± 0.8*** | ***13.2 ± 1.0*** | ***13.6 ± 1.0*** | ***14.1 ± 1.2†*** |
| HyperPL | | 12.0 ± 1.2 | 12.4 ± 1.0 | 12.8 ± 1.1 | 12.9 ± 0.8 | 13.8 ± 1.0 | 14.5 ± 1.1 | 15.1 ± 1.4 | 15.6 ± 1.7 |
| HyperBB | | 12.3 ± 1.3 | 12.5 ± 1.4 | 13.0 ± 1.0 | 13.2 ± 1.3 | 13.9 ± 1.1 | 14.7 ± 1.1 | 15.3 ± 1.3 | 16.0 ± 1.7 |
| ***HYPER*** | | ***12.2 ± 1.2*** | ***12.4 ± 1.2*** | ***12.9 ± 1.0*** | ***13.0 ± 1.1*** | ***13.8 ± 1.0**** | ***14.6 ± 1.1**** | ***15.2 ± 1.3**** | ***15.8 ± 1.7*†*** |

Values are mean ± SD of 11 subjects for O2 uptake (VO2), cardiac output (CO), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), total peripheral resistance (TPR), mean skin temperature (Tskin), forearm blood flow (FBF), rating of perceived exertion (RPE), and cutaneous blood flow (CBF), during 60 min of exercise at ~57% of VO2max. For Q, DBP, MAP, TPR, FBF, CBF, and RPE there were no main effects between NormoPL and NormoBB or between HyperPL and HyperBB; therefore, data was pooled from NormoPL + NormoBB (NORMO) and from HyperPL + HyperBB (HYPER) in order to compare the effect of normothermia vs. hyperthermia. For SBP data was pooled from NormoPL + HyperPL and NormoBB + NormoPL in order to compare the effect of the placebo vs. beta blockade (BB).Measures of FBF were made at rest, 12, 35, and 55 minutes of exercise. * Indicates significant difference between NORMO and HYPER, for SBP * Indicates significant difference between Placebo and BB. † Indicates significant difference from min 10, $p < 0.05$.

Table 3.2: *Bodyweight changes pre to post exercise, fluid intake, and sweat volume*

| | NormoPL | NormoBB | HyperPL | HyperBB |
|---|---|---|---|---|
| Pre Bodyweight (kg) | 77.9 ± 11.5 | 77.7 ± 11.6 | 77.8 ± 11.9 | 77.5 ± 11.5 |
| Post Bodyweight (kg) | 77.9 ± 11.5 | 77.8 ± 11.6* | 77.6 ± 11.8* | 77.3 ± 11.4* |
| % Change in BW (%) | -0.02 ± 0.26 | 0.13 ± 0.19 | -0.21 ± 0.25 | -0.26 ± 0.25 |
| Fluid intake (l) | 1.272 ± 0.405 | 1.272 ± 0.405 | 1.624 ± 0.346† | 1.624 ± 0.346† |
| Sweat Volume (l) | 1.286 ± 0.441 | 1.172 ± 0.376 | 1.787 ± 0.553† | 1.824 ± 0.529† |

Values are mean ± SD of 11 subjects. Measurements of bodyweight were made pre and post exercise. * Indicates significant difference from pre bodyweight, † indicates signifcance from NormoPL and NormoBB, $p < 0.05$.

Table 3.3: *Percent change in blood and plasma volume during exercise*

| | 5 | 15 | 30 | 45 | 60 |
|---|---|---|---|---|---|
| Δ BV, % | | | | | |
| NormoPL | -5.4 ± 2.4 | -5.1 ± 2.8 | -5.8 ± 3.6 | -5.3 ± 3.0 | -4.2 ± 3.9 |
| NormoBB | -5.4 ± 4.1 | -6.6 ± 3.9 | -7.3 ± 3.7 | -7.0 ± 3.6 | -6.1 ± 2.7 |
| HyperPL | -7.1 ± 2.7 | -6.3 ± 3.7 | -5.8 ± 3.8 | -6.4 ± 3.6 | -5.7 ± 4.3 |
| HyperBB | -6.4 ± 2.2 | -6.7 ± 2.3 | -7.2 ± 2.2 | -6.5 ± 2.2 | -6.8 ± 3.0 |
| Δ PV, % | | | | | |
| NormoPL | -9.2 ± 4.1 | -8.8 ± 4.5 | -8.7 ± 6.0 | -8.2 ± 5.0 | -6.5 ± 6.9 |
| NormoBB | -8.9 ± 5.8 | -10.3 ± 3.9 | -11.0 ± 4.0 | -10.1 ± 4.8 | -8.1 ± 3.2 |
| HyperPL | -12.3 ± 4.4 | -10.2 ± 5.6 | -9.5 ± 5.6 | -10.1 ± 6.3 | -8.6 ± 5.9 |
| HyperBB | -10.4 ± 3.0 | -9.8 ± 4.2 | -10.8 ± 3.6 | -10.3 ± 3.0 | -10.6 ± 4.4 |

Values are mean ± SD of 9 subjects, percent change in blood volume from rest (Δ BV, %) and percent change in plasma volume from rest (Δ PV, %). All differences were significant from rest, $p < 0.05$.

# CHAPTER VII: REVIEW OF RELEVANT LITERATURE

## *1 – Cardiovascular Drift during Prolonged Exercise*

Cardiovascular (CV) drift is characterized by the progressive increase in HR and decrease in SV and MAP, while Q remains relatively constant. The underlying cause of the CV drift is controversial. One hypothesis is that the peripheral displacement of blood to increase cutaneous blood flow causes a progressive fall in central venous pressure, SV and MAP (Rowell *et al.*, 1969a; Rowell *et al.*, 1969b; ROWELL *et al.*, 1969; Rowell, 1986, 1993). The alternate hypothesis is that the progressive increase in HR caused by hyperthermia and/or increased sympathetic nervous system activity decreases ventricular filling time and end diastolic volume (Gonzalez-Alonso *et al.*, 2000).

### *1a: Classic CV Drift*

The original hypothesis for the peripheral displacement of blood to cause CV drift was developed based on experimental evidence during exercise in extreme heat of 43.3 ºC and with minimal air movement or evaporative cooling of the skin. Under such conditions skin temperature may have been elevated to the point where venous pooling in the skin may have occurred as skin temperature under these conditions may be greater than 38 ºC (ROWELL *et al.*, 1969; Rowell, 1986) (skin temperature is assumed as it was not directly measured in the original investigation;(Rowell *et al.*, 1966). The alternate hypothesis was developed under thermal conditions similar to what may be

encountered during actual exercise in the heat with skin allowed to cool to 31-34°C by the evaporation of sweat, and therefore may be more appropriate for application to typical exercise performed without protective garments (e.g.; fire fighting suits, hazardous material garments, football uniforms and pads, etc…)

*1b: Environment, Exercise Intensity, Dehydration*

The foundation for the alternate hypothesis comes from the work of Coyle and colleagues (González-Alonso *et al.*, ; Gonzalez-Alonso *et al.*, 1997; Fritzsche *et al.*, 1999; González-Alonso *et al.*, 1999; Gonzalez-Alonso *et al.*, 2000). During two hours of exercise that caused dehydration and hyperthermia, declines in SV and CO were confirmed (Montain & Coyle, 1992a). During similar exercise bouts skin blood flow was found to be severely compromised due to cutaneous vasoconstriction as a result of a catecholamine response (Mora-Rodriguez *et al.*, 1996) that appears to be triggered by declining arterial blood pressure (Gonzalez-Alonso *et al.*, 1999; Coyle & Gonzalez-Alonso, 2001). The failing cardiovascular system was attempting to attenuate reductions in blood pressure through peripheral vasoconstriction (i.e.; increased TPR). Skin blood flow was particularly reduced and core temperature increased dramatically as the body attempted to balance the immediate need to maintain arterial blood pressure versus the need for heat dissipation, that can't be forestalled for more than 5-15 min without severe hyperthermia (Montain & Coyle, 1992b; Gonzalez-Alonso *et al.*, 1995; Coyle & Gonzalez-Alonso, 2001). A main outcome of these studies was to counter the prevailing

thinking that SV is reduced due to increased skin blood flow and pooling of blood in veins and thus reduced venous return (Coyle & Gonzalez-Alonso, 2001). This initial work regarding CV drift during prolonged exercise led to the question of what causes the 10 to 30% reductions in SV and CO during the 15 to 120 minute period of exercise resulting in hyperthermia that is performed in the upright or supine position. This remains only partially answered; however, recent work by Dawson et al. (Dawson *et al.*, 2005) provides echocardiographic evidence that reduced diastolic function may lead to cardiovascular drift during prolonged exercise.

The works of Coyle and colleagues in the late 1990's were designed to measure SV and cardiovascular drift in athletes after two hours of exercise in a hot environment subsequent to reversing extra-myocardial factors (e.g.; body position and blood volume) that might be responsible for part of the large reduction in SV observed during upright exercise (Coyle & Gonzalez-Alonso, 2001). Indeed, dehydration and reductions in blood volume accounted for part of the reduction in SV (Montain & Coyle, 1992a; Gonzalez-Alonso *et al.*, 1997). Body position during cycling (upright *vs.* supine) influences venous return due to gravity as measured by left ventricular end-diastolic volume and SV (Martin *et al.*, 1986). Positioning the heart below the legs with supine exercise reversed approximately one-half of the decline in SV observed with the cardiovascular drift and hyperthermia of prolonged exercise (Gonzalez-Alonso *et al.*, 1999). Furthermore, heart rate elevation during exercise at a given power output appears to reduce SV (Fritzsche *et al.*, 1999; Gonzalez-Alonso *et al.*, 1999), possibly by reducing ventricular filling time.

No attempts were made to manipulate myocardial afterload because under conditions of cardiovascular failure, afterload (systolic blood pressure) was not increased as reflected by arterial pressure and rough indices of ventricular wall stress (Coyle, 1998; Gonzalez-Alonso *et al.*, 1999). The reductions in systolic blood pressure with cardiovascular failure during exercise and thus reduced afterload should attenuate reductions in SV. This suggests that reduce cardiac function (cardiac fatigue) might be underestimated as it appears to be naturally compensated by reduced afterload.

These studies were of utmost importance because they systematically identified the contribution of extra-myocardial factors (i.e.; blood volume, body position; ventricular filling time, arterial pressure) that must be controlled during exercise in order for SV to be limited by heart function per se. Based upon the results of the aforementioned studies it became apparent that hyperthermia alone caused marked reductions in SV (Gonzalez-Alonso *et al.*, 1997; Gonzalez-Alonso *et al.*, 2000). It could not be determined if this was due to myocardial or extra-myocardial factors as cardiac images were not obtained. However, three important points became clear. First, the reductions in SV after 2 h of exercise could be entirely reversed by expanding blood volume to normal euhydrated levels as long *as hyperthermia was prevented* (Gonzalez-Alonso *et al.*, 1999, 2000; Coyle & Gonzalez-Alonso, 2001). This indicated that if reductions in SV were due to cardiac fatigue then the fatigue was not chronic and it could be reversed in a matter of minutes. This indicates that the cause of cardiovascular failure was acute and implies it was not due to substrate depletion of myocytes or

protein denaturing. Second, it became clear that countermeasures against cardiovascular failure, involving cooling and blood volume expansion, can allow a person to resume intense exercise in a matter of minutes after experiencing acute cardiovascular fatigue (Gonzalez-Alonso *et al.*, 1999). Third, hyperthermia always elicited reductions in SV and some degree of cardiovascular fatigue even when blood volume was increased (21) or exercise was performed in the supine position (Gonzalez-Alonso *et al.*, 1999).

*1c. Effect of Body Position*

Body position plays an important role in the attempt to determine the underlying cause of reduced cardiac function during exercise. Gonzalez-Alonso et al. (González-Alonso *et al.*) had subjects exercise at 62% of VO2max in the heat (35°C) while either euhydrated or dehydrated by 5% and in both the supine and upright positions. Dehydration elicited similar hyperthermia independent of exercise position (+ 0.8°C). Supine exercise attenuated the increase in HR (7 *vs.* 9%), the reduction in SV (13 *vs.* 21%), and the reduction in CO (8 *vs*. 14%). During supine exercise with dehydration skin temperature was 1°C higher during supine exercise compared to the upright trial. This increase in skin temperature during supine exercise is most likely to the fact that the skin of the back is not exposed to fan cooling. The reductions in MAP and cutaneous vascular conductance and the increase in NE observed with dehydration and

hyperthermia during upright exercise were totally absent during supine exercise. Despite this finding SV was still reduced even in the supine positions.

*1d. Role of Plasma Volume on Cardiovascular Drift*

One of the most rapid physiological adaptations to exercise training is an increase in blood volume. Similarly, during detraining the expanded blood volume of athletes is one of these first adaptations that is lost (Coyle *et al.*, 1984; Coyle *et al.*, 1986). When PV expansion is induced by only 3 to 4 days of training (Green *et al.*, 1990) or with training and acclimatization (Mitchell *et al.*, 1976; Senay *et al.*, 1976; Wyndham *et al.*, 1976) little effect on the CV or thermoregulatory changes is observed beyond the early adjustment period to exercise. It is only when the training period is extended that the CV and thermoregulatory events appear to be modified with exercise time (Mitchell *et al.*, 1976; Wyndham *et al.*, 1976; Convertino, 1991). Too large of an increase in PV may increase blood flow to working muscle due to hemodilution and reduction in arterial O2 delivery (Kanstrup & Ekblom, 1982; Convertino, 1991).

A series of studies (Mitchell *et al.*, 1976; Senay *et al.*, 1976; Wyndham *et al.*, 1976) examined the effects of acclimatization in a hot and humid environment found that cardiovascular adjustments follow a predictable time course with four distinct phases. Exercise on day 1 was characterized by a fall in SV and a high HR. During days 2 to 3 SV increased and HR decreased with little change in CO. After 4 to 8 days CO increased due to an increased SV and not until days 6 to 8 did Trec and Tskin return

toward control levels. It is important to note that events occurring during the first 4 days had little effect on body temperature. Green et al. (Green *et al.*, 1990) showed similar results in that that 3 days of training for 2 hours per day at 65% of VO2max resulted in a 20% increase in plasma volume and a 12% increase in blood volume (BV). These increases in PV and BV corresponded to an increase in SV of 22ml/beat and a reduction in HR. Despite these large changes in CV function there appeared to be no benefit on thermoregulatory behavior. After the first few days of exercise that hypervolemia that accompanies the acclimatization may provide advantages of greater body fluid for heat dissipation and thermoregulatory stability. Furthermore, the increase in vascular volume increases filling pressure which can lead to increased SV and reduced HR (Convertino, 1991).

*1e. Effect of Cardiovascular Drift on Maximal Exercise Capacity*

Cardiovascular drift has recently been shown to reduce VO2max. Wingo et al. (Wingo *et al.*, 2005; Wingo & Cureton, 2006a, b) showed VO2 max was reduced (19%) in proportion to the amount of CV drift (12% increase in HR and 16% in SV) that occurred from 15 to 45 minutes of exercise under hot environmental conditions without fan cooling. The cause of the decrease in VO2max is not entirely clear as SV was unable to be measured during the incremental exercise VO2max test. Cardiac function appears to be maximal as HR was similar at fatigue under. Interestingly, core temperature at 45 minutes of exercise was elevated by 1º C when compared to 15 minutes of exercise,

which is same elevation of core temperature induced by preheating in the study by Gonzalez-Alonzo et al. (Gonzalez-Alonso & Calbet, 2003b). Based upon the assumption that local muscle fatigue during the 30 minute exercise at a moderate intensity (60%) did not cause the reduced VO2max and the findings that skin temp was the same these studies effectively isolated the effect of elevated core temperature on VO2max.

Overall, under conditions eliciting hyperthermia, cardiac drift occurs as evidenced by an elevated HR and reduced SV during constant workload cycling. Environmental changes such as increases in ambient temperature and relative humidity will influence the degree of cardiovascular drift as cardiac output is elevated and cutaneous blood flow is increased. Stroke volume is reduced even under conditions that maximize venous return (supine exercise) indicating that cardiac function is lessened. The underlying reason for this reduction in cardiac function may be due to altered contractility of the myocardium or reduced ventricular filling and performance.

### *2- Cardiovascular Function with B-blockade*

*2a. High-dose BB (acute vs. chronic)*

B-adrenergic blocking agents are used in the treatment of cardiovascular diseases including angina pectoris and hypertension. Individuals with symptoms or risk factors of cardiovascular disease are routinely prescribed exercise in combination with

BB. B-blockers act to block the sympathetic effect of hormones, primarily epinephrine. Therefore, the cardiovascular response to exercise with BB will be altered when compared to normal exercise conditions. Cardiovascular compensation with BB include the following; decrease in HR (~25%), increase SV, increase in a-vO2diff. BB decreases HRmax and increases SVmax while CO is generally maintained. When VO2max is < 45 – 50 (ml/kg/min) BB does not appear to reduce VO2max (Anderson *et al.*, 1985; Tesch, 1985; Wilmore *et al.*, 1985; Joyner *et al.*, 1986; Jilka *et al.*, 1988; Kalis *et al.*, 1988; Mier *et al.*, 1997a). When VO2max is higher > 50 (ml/kg/min) BB appears to reduce VO2max by about 10%. There is a limit to the compensation by SV and avO2diff. In addition to the cardiovascular effect of BB, BB also effects Thermoregulation. Individuals on BB exhibit a lower FBF for any given Tcore. BB also enhances sweat loss and a lower Tskin (Gordon *et al.*, 1985; Freund *et al.*, 1987). The reduction in FBF at any given Tcore was concomitant to lower blood pressure, suggesting that baroreflexes provide significant input to control of skin blood flow.

*2b. Minimal dosage to alter SV and HR response to exercise*

Large doses of BB have substantial impact on CV function and exercise capacity. However, a few investigators have used low doses of BB to alter the normal response to exercise in order to control cardiovascular responses to exercise. Pawelczyk et al. (Pawelczyk *et al.*, 1992) gave subjects 0.2mg/kg metoprolol and effectively reduced cardiac output (19%) and leg blood flow (11%) to the active muscle. This study was

designed to determine whether or not leg vasoconstriction occurs when cardiac output is reduced. The authors concluded that neurogenic vasoconstriction evidenced by an increase in NE spillover under BB can offset metabolic vasodilation during intense exercise when cardiac output is compromised. Fritzsche et al. (Fritzsche *et al.*, 1999) gave subjects 0.1mg/kg atenolol immediately prior to exercise in order to alter the CV response to prolonged exercise. Under normal conditions (ie; no BB) CV drift occurred as HR increased and SV decreased. BB was able to completely block the normal increase in HR after the initial 15 minutes of exercise. The attenuation of the increase in HR and decrease in SV abolished the CV drift observed under control conditions. CV drift was not correlated to forearm blood flow as FBF was the same in both conditions. Based on the findings of this study it is evident that under conditions where skin temp is relatively low (31.5 C) and core temp is low (37.8 C) CV drift occurs because of the progressive increase in HR. It has been proposed that this increase in HR reduced diastolic filling time and EDV leading to a reduction in SV.

### ***3 - Core temperature and fatigue***

#### *3a. Critical Core Temperature and Fatigue*

Evidence that Q and skeletal muscle blood flow is the limiting factor in maintaining exercise at VO2max comes from the invasive investigations of Gonzalez-Alonso and colleagues (Gonzalez-Alonso *et al.*, 2001; Gonzalez-Alonso & Calbet, 2003b;

Gonzalez-Alonso *et al.*, 2004; Mortensen *et al.*, 2005). Subjects performed exercise at workloads eliciting VO2max under normal and hyperthermic (elevation of core temperature by 1º C) conditions in order to determine the central cardiovascular responses to the fatigue process. The main finding of this study was that the pattern of fatigue was similar in both the normal and hyperthermic conditions with the heat stress decreasing VO2max and accelerating the decrease in Q, and MAP, that lead to the decrease in locomotor blood flow, O2 delivery and O2 uptake. This decline in skeletal muscle VO2 was solely attributed to the decrease in systemic and skeletal muscle O2 delivery as the arterial O2 content, leg O2 extraction, and leg vascular conductance were unaltered. Heat stress increased Q (~1.5 l/min) and decreased leg blood flow (0.7 – 2.7 l/min); however, VO2 at the leg was similar as CaO2, a-vO2diff, and O2 extraction were increased. Similar adjustments to decreasing O2 delivery have been determined under conditions of anemia and hypoxia. These findings also argue against a diffusion limitation to maintaining exercise at VO2max as leg a-vO2diff and O2 extraction increased progressively until the end of exercise.

These findings show that cardiac fatigue is occurring during high intensity exercise and in a manner remarkably similar to the prolonged exercise bouts in the heat that cause cardiovascular drift (references from above). The decline in Q, leg blood flow, and MAP occurred before maximal HR was achieved indicating that maximal CV function can be attained below max HR. The inability to maintain SV appears to be the main reason for the decline in cardiac function. The decline in SV coincided with the decrease

in MAP, a core temperature of greater than 39 C, and an almost maximal HR. The lowered MAP rules out the influence of altered afterload contributing the reduced SV. Therefore, preload and myocardial contractility appear to be responsible for the decreased SV although no direct evidence is available.

The central limitation to aerobic power and capacity has been further advanced by the work of Mortenson et al. (Mortensen *et al.*, 2005). Systemic hemodynamics, O2 transport and O2 uptake were measured during incremental exercise to exhaustion, constant load cycling to exhaustion, and one leg knee extension to exhaustion. During incremental cycling to exhaustion systemic and locomotor O2 delivery did not increase linearly from rest to VO2max but plateaued at approximately 80% of VO2max. Similarly, vasoconstriction as evidenced by the plateau and non-significant decline in leg vascular conductance at 80% of VO2max. Oxygen extraction at the working muscle continued to increase despite a concomitant plateau in O2 delivery. Under constant load cycling at a workload eliciting VO2max, O2 delivery and VO2 declined 3% prior to exhaustion. During the final portion of the exercise bout, just prior to exhaustion CO declined approximately 7%. The reduction in the O2 delivery in both cycling exercise was associated with the fall in SV when core temperature was highest (39.5º to 39.9º C). In contrast, during one leg knee extension under conditions where leg blood flow (l/kg/min) was 3 to 4 fold higher than cycling and oxygen delivery was not limited, leg blood flow and VO2 increased linearly until exhaustion.

The underlying mechanism regulating the critical core temperature and fatigue may be related to dopamine and noradrenaline levels in the hypothalamus (Hasegawa *et al.*, 2008). In order to understand this mechanism Watson et al. (Watson *et al.*, 2005) had subjects perform 4 trials consisting of 60 minutes of exercise at 55% Wmax followed by a time trial under placebo or bupropion treatments. Buproprion, a dopamine and noradrenaline reuptake inhibitor, may act on central DA and NA neurotransmission to maintain motivation and arousal, enabling subjects to sustain a higher power output despite approaching the critical core temperature (Watson *et al.*, 2005; Hasegawa *et al.*, 2008). During the time trial in the heat Tcore was 0.3°C higher and HR 5 bpm higher under bupropion. The authors conclude that the drug may dampen or override inhibitory signals arising from the CNS to cease exercise due to hyperthermia and enable an individual to continue to maintain a high power output.

*3b. Evidence against a Critical Core Temperature*

The tight relationship between core temperature and fatigue has drawn criticism from numerous researchers. Two alternative hypotheses argue against a critical core temperature as the cause of fatigue. One of these hypothesis states that the ability to tolerate high core temperatures is likely dependent upon the athlete's skin temperature, as warmer skin (warmer environment) creates greater circulatory strain and lowers core temperature tolerance (Kenefick *et al.*, 2007). This theory is physiologically viable as many thermoregulatory responses depend on both core and

skin temperature: at any given skin temperature, each thermoregulatory response is proportional to esophageal temp, and increasing the skin temp lowers the threshold level of esophageal temp and increases the response at any given core temp ((Michael N Sawka, 1988)Sawka and Wenger). However, research relating this core to skin temp gradient to actual exercise performance is limited. The other argument states that the rate of heat production may be more important than the actual core temperature in the development of fatigue (Noakes, 2000; Noakes *et al.*, 2001; Noakes *et al.*, 2004; Noakes & St Clair Gibson, 2004; Tucker *et al.*, 2004; Tucker *et al.*, 2006). This hypothesis is based on the anticipatory regulation of exercise intensity or duration based on the initial rate of heat storage thus allowing the individual to avoid catastrophe.

*3c. Rate of Heat Production as a Critical Factor*

The rate of heat storage and the skin to core temp gradient was addressed by Gonzalez-Alonso et al. (González-Alonso *et al.*, 1999). The rate of heat storage was altered by having subjects exercise with and without a jacket. Rate of heat storage was either 0.05 or 0.10 °C/min. Despite the difference in rate of heat production and the higher Tskin (38.4 vs 35.6°C) exhaustion occurred at the same core temperature. While the rate of heat production was drastically different skin temp may consider high under both conditions (> 35 C). Based on research by Cureton (Arngrimsson *et al.*, 2003; Wingo *et al.*, 2005; Wingo & Cureton, 2006a, b) and colleagues skin temperature may have to be above 33 to 34°C in order to affect cardiac function during exercise, therefore the

skin temps of Gonzalez-Alonso (González-Alonso *et al.*, 1999) may not have different physiological effects. Similarly, well trained individuals with high aerobic fitness appear to be able to tolerate hyperthermia and perform longer in uncompensable hot environments better than untrained and moderately trained (Cheung & McLellan, 1998). Therefore, the relationship between core temp and fatigue may not be applicable to all subjects.

*3d. Hyperthermia and the Myocardium*

In all cases, prolonged exercise in the heat as well as during high intensity exercise at VO2max, cardiovascular failure occurred when core temperature approached 40º C. This was the case when intense exercise (95% $VO_2$max) was maintained for 7-8 min under control or when the participants began with elevated core temperature and fatigued after 5 min (Gonzalez-Alonso & Calbet, 2003a), or when the intensity is lower (65% $VO_2$max) and elicits hyperthermia after 120 min when significant dehydration is experienced (Coyle & Gonzalez-Alonso, 2001). It has been well established in isolated heart and myocytes that elevated temperature markedly reduces contractile function (Ranatunga, 1994; Saeki *et al.*, 2000; Janssen *et al.*, 2002; Hiranandani *et al.*, 2006). Saeki et al. (Saeki *et al.*, 2000) showed that hyperthermia causes a negative inotropism (decrease in force development) and an increase in the oxygen cost of contractility by approximately 1.5 fold. The depressed left ventricle contractility during hyperthermia appears to be largely due to a decrease in calcium

responsiveness to the contractile protein. Janssen et al. (Janssen *et al.*, 2002) demonstrated that under hyperthermic (42º C) conditions force development of the isolated myocyte is reduced by 67% when compared to normothermia (37º C). Despite this substantial reduction in developed force, relaxation rate is accelerated and may partially offset the reduction in force development at high stimulation frequencies. Therefore, it is quite possible that hyperthermia of the blood and heart is the primary factor that causes reductions in SV, BP, CO and reduced oxygen delivery to the leg muscles. It seems that hyperthermia might simply reduce myocardial contractile function.

***4 - Cardiovascular responses to various skin temperatures.***

Skin and muscle blood flow are first and foremost determined by cardiac output. Therefore it is critical to understand how rapidly changing one of these variables (skin blood flow or muscle blood flow) influences CO. Despite this logic only a few studies have manipulated skin and core temperature independently of one another in order to determine the control and regulation of CO. The rationale for such a protocol originates from pilot work in our lab. During exercise when heat stress is removed and evaporative cooling is allowed to function Tskin drops from 36 to 27 C in a matter of 2 to 3 minutes. During this same time period Tcore remains elevated as the rate of metabolic heat production is maintained. Therefore, using such a design conditions of [high core & low

skin temp], [low core & high core] can be compared to [high core & high skin] and [low core & low skin] paradigms. Rowell et al. (ROWELL *et al.*, 1969) had subjects exercise at low (26% of VO2max) and moderate workrates (64% of VO2max) while wearing a suit perfused with different water temperatures. Water temperature of the suit was 32 C for the first 30 minutes, 40 C during the 30 to 60 minute period, 10 C during the 60 to 90 minute period and then 50 C during the final stage of exercise. Upon switching from 32 to 40°C water during the moderate intensity trials Tskin increased from 32 C to 38.7 C. During this time CO increased 19% and SV was reduced by 14%. Interestingly the decrease in HR upon cooling appears to directly relate to the reduction in blood temperature and presumably skin temperature (although not reported). SV on the other hand remains partially reduced during the first 10 minutes of the transition period as core temperature remains elevated. Increases in CO during heating were related to skin temperature and not to VO2 or body temperature. Due to the fact that this study was not specifically designed to isolate skin and core temperature it is difficult to draw conclusions based on this topic from these results.

As alluded to in the previous section evaporative cooling plays a large part in skin and core temperature. Exercise with a water perfused suit removes any evaporation that may occur during normal exercise for portions of the body covered by the suit and not exposed to moving air. Shaffrath and Adams (Shaffrath & Adams, 1984) investigated the effect of airflow and work load on CV drift and skin blood flow. Moderately trained individuals (58 mlO2/kg/min) exercised for 70 minutes under relatively cool conditions

(24.2°C and 40%RH) at 40 and 60% of VO2max with fan speeds of 4.3 or 0.2m/sec. Under conditions of low airflow during the 60% VO2max trial HR increased 21.6 bpm, SkBF increased 14%/min, SV decreased 16.4 ml and MAP decreased 11.3 mmHg. Skin temp at 60% of VO2 max under fan cooling was 28.5° C while without fan is ~32°C (Δ ~3.5 °C), Trec was only ~ 0.3° C different between the conditions, Therefore it is likely that the lower Tskin results in lower FBF and therefore no CV drift. In one subject (triplicate data) turning the fan on at minute 70 reversed a portion of the CV drift as evidenced by the 10 bpm reduction in HR from minute 70 to 75.

***5 – Stroke Volume Response to Graded and Constant Load Exercise***

*5a. Stroke Volume Plateau / Decline during Incremental and Constant Load Exercise*

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decrease in locomotor blood flow, O2 delivery and O2 uptake. This decline in skeletal muscle VO2 was solely attributed to the decrease in systemic and skeletal muscle O2 delivery as the arterial O2 content, leg O2 extraction, and leg vascular conductance were unaltered. Heat stress increased Q (~1.5 l/min) and decreased leg blood flow (0.7 – 2.7 l/min); however, VO2 at the leg was similar as CaO2, a-vO2diff, and O2 extraction were increased. Similar adjustments to decreasing O2 delivery have been determined under conditions of anemia and hypoxia. These findings also argue against a diffusion limitation to maintaining exercise at VO2max as leg a-vO2diff and O2 extraction increased progressively until the end of exercise.

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Recently Calbet et al. (Calbet *et al.*, 2007) examined the CO and leg and arm blood flow response during incremental exercise to exhaustion. Invasive techniques were employed to directly measure CO and SV. Similar to Mortenson et al. (Mortensen *et al.*, 2005) CO increased curvilinearly up to 84% of Wmax, CO only increased 1.2 L/min

from 84 to 100% of Wmax. However, unlike Mortenson et al. SV stabilized at approximately 50% of Wmax and did not decline prior to exhaustion. The authors recognized this discrepancy and believe the lower MAP and difference in the exercise protocols between the two investigations may account for the different SV response. Beck et al. (Beck *et al.*, 2006) showed that a subset of subjects exhibited a negative curvature for both HR and SV during progressive exercise to exhaustion and that this negative curvature may indicate a Q limitation to VO2max. Similarly, Stringer et al. (Stringer *et al.*, 2005) determined that a curvilinear fit was more appropriate than a linear fit in describing the VO2 to Q relationship. Fundamental aspects of human physiology such as the CO and VO2 relationship as well as the HR and workload relationships may need to be re-examined as more data is collected in subjects exercising at high intensities. Generally data describing these fundamental relationships are made at low and moderate exercise intensities thus yielding apparent linear relationships; however, most competitive events are won or lost at exercise intensities above 80% of VO2max with the exception of ultra-endurance events.

*5b. Stroke Volume does not Decline During Exercise*

Warburton and Gledhill (Gonzalez-Alonso *et al.*, 2007) argue in a recent point-counterpoint in the Journal of Applied Physiology that “only the least fit exhibit a decrease in SV at higher intensities; a pattern that is consistent with reduced myocardial compliance and marked pericardial constraint.” It is their assertion that endurance

exercise training causes specific adaptations to the cardiovascular system that attenuates the reduction in SV observed in untrained individuals. These training related adaptations include; increased myocardial compliance, reduced diastolic ventricular interaction, increased LV internal cavity, increase early filling (E/A ratio), increased transmitral pressure gradient and flow velocity, hypervolemia, increased rate of LV pressure decline, increased rate of calcium uptake in SR. Despite the scientific evidence provided by these authors the method in which maximal exercise was performed may give rise to spurious cardiovascular responses. Gledhill et al. (Gledhill *et al.*, 1994), the first investigation from this group, showed that endurance athletes posses a continual increase in SV up to maximum and that this response is primarily due to enhanced diastolic function. However, methodological considerations must be examined. First, each stage of the progressive exercise test consisted of four minutes. VO2 was determined during the end of the second minute (90 to 120 sec) while CO was performed in triplicate via acetylene rebreathing during the final two minutes (120 to 240 sec) of each stage. Under ideal conditions VO2 and CO measurements would be made at the same time. VO2 may continue to drift during high intensity exercise thereby altering the VO2 vs. CO relationship. VO2 and CO were determined during the progressive test. As recently reviewed by Rowland (2008) the non-conventional supramaximal testing protocol of Gledhill and colleagues appears to alter the SV to HR relationship established during the standard progressive test to exhaustion. After subjects completed the standard progressive test to exhaustion they were given one

minute to rest before pedaling again at a supramaximal workload. It was during this supramaximal stage that CO, HR, and VO2 were defined as maximum. After investigating this data it is clear that this final supramaximal stage interrupts the apparent plateau established by the progressive test. Warburton et al. (Warburton *et al.*, 2002) demonstrated a similar SV response in well trained endurance athletes and concluded that enhanced diastolic function manifested by progressive increases in diastolic filling rate and EDV allow endurance trained athletes to increasingly use the Frank-Starling mechanism throughout incremental to maximal exercise. These authors conclude that chronic volume overload placed on the myocardium by athletes who repeatedly exercise at large SV and CO may lead to morphological and functional adaptations allowing for the progressive utilization of the Frank-Starling mechanism.

*5c. Effect of Exercise Training on the Stroke Volume Response to Exercise*

Longitudinal exercise training studies provide insight regarding the malleability of the SV response in a given individual. Spina et al. (Spina *et al.*, 1992) determined that exercise training prevented the decline in SV during exercise in young healthy adults. Prior to training SV at VO2max was 9% lower than during exercise at 50% of VO2max indicating a clear reduction in SV from submaximal to maximal exercise. Following training CO increased 12%, SV increased 16% and HR was reduced at the same exercise intensity. Furthermore, SV was only 2% lower at VO2max than 50% VO2max following

training. This minor reduction in SV was not significantly and most likely within the error of the acetylene rebreathing technique. The mechanism responsible for the attenuation of the SV response is not entirely clear but appears to involve increased blood volume which augments left ventricular filling, and or altered diastolic properties of the myocardium.

Short term endurance training of 6 to 10 days also effects the SV response to exercise. Goodman et al. (Goodman *et al.*, 2005) exercise subjects for 2 hours at 65% of VO2max for 6 consecutive days. Training increased PV 11.4%, increased VO2max from 45.9 to 49 ml/kg/min, and decreased HRmax by 9 bpm (197 – 188 bpm). Following the training regimen SV was 10.4, 10.2, and 7% higher at 53, 68, 83% of VO2max and was accompanied by substantial bradycardia at each workload. EDV increased significantly and increases in SV were secondary to a Frank-Starling effect with minor changes in contractile performance. Mier at el. (Mier *et al.*, 1997b) demonstrated the LV contractile performance, assessed by relating fraction shortening to estimated end systolic wall stress, was improved by 10 days of endurance training.

There is currently much debate regarding whether or not SV declines during maximal exercise (Gonzalez-Alonso *et al.*, 2007). The argument is centered on the SV response to incremental exercise, however of greater relevance to this review is the SV response during constant load maximal exercise. Numerous factors such as body position during exercise (supine vs. upright), instrumentation for the determination of

SV (inert gas rebreathing, direct fick, thermodilution, echocardiography, etc…), subject training status (highly trained, trained, untrained), and the timing of the measurements during exercise may account for the differences observed in the literature. Critical to the purpose of this review is the determination of whether or not SV declines during constant load cycling at VO2max. This protocol (constant load cycling at VO2max) allows for the assessment of the capacity of the cardiovascular system to sustain systemic and locomotor blood flow (Gonzalez-Alonso & Calbet, 2003b; Gonzalez-Alonso *et al.*, 2004; Mortensen *et al.*, 2005; Gonzalez-Alonso *et al.*, 2007). It is therefore paramount that physiological measurements (VO2, SV, CO, HR, BP) be made prior to the development of fatigue and just prior to exhaustion. To date, only a few studies have made such measurements (Gonzalez-Alonso & Calbet, 2003b; Gonzalez-Alonso *et al.*, 2004; Mortensen *et al.*, 2005) and have showed reductions in SV and Q prior to exhaustion. The cause of this decline in SV may be due to reduced preload and/or reduced left ventricular function.

# APPENDIX A:

***Indirect Calorimetry (Study 1):*** Subjects breathed through a two-way valve connected to a pneumotachometer (Hans Rudolph, Kansas City, MO) to measure inspiratory air volume (VI; l/min). Expired air was sampled continuously from a mixing chamber and analyzed for O2 (FeO2; Ametek CD-3A) and CO2 concentrations (FeCO2; Beckman LB-2). Both analyzers and the pneumotachometer were interfaced to a laboratory computer (Dell) with an A/D board (Physiodyne). The gas analyzers were calibrated before every measurement period using gases of a known concentration (15% O2, 5% CO2). Oxygen consumption (VO2; L/min) was calculated as: VO2 = (VI x 0.2093) - (VE x FeO2) where VE = expired air volume (L/min). Carbon dioxide consumption (VCO2; L/min) was calculated as: VCO2 = (VE x FeCO2) - (VI x 0.0003). The VE and VI values used in the above equations were standardized to STPD (L/min). VE was calculated using the Haldane transformation as: VE = VI x [(1 - FeO2 - FeCO2)/0.7903]. Respiratory exchange ratio (RER) (non-protein) was calculated as: RER = VCO2/VO2.

***Gross efficiency (Study 1):*** Gross efficiency (GE) was calculated as the ratio of work accomplished per minute (i.e.; watts converted to kcal/min) to energy expended per minute (kcal/min). Energy expenditure per min (i.e.; kcal/min) was calculated from VO2 and RER using the table of Lusk (Lusk, 1924). VO2 used in the calculation of GE was the average value of the final minute of each workrate.

## APPENDIX B:

***Body Temperature Calculations:*** Core temperature (Tcore) was measured using a rectal temperature probe (model 401, Yellow Springs Instrument) inserted 12 cm past the anal sphincter. A subset of subjects in study 2 performed esophageal core temperature measurements (Teso) in combination with the rectal temperature measurement. The esophageal probe (model 4491, Yellow Springs Instruments) was inserted through the nasal passage and swallowed to depth of one-fourth of the subject's standing height (Mekjavic 1990). Skin Temperature (Tskin) was measured using skin thermistors (model 409A, Yellow Springs Instrument) at six sites; back, chest, bicep, forearm, thigh and calf and mean Tskin was calculated based on a modified equation of Hardy and Dubios (Hardy *et al.*, 1938).

Tskin = 0.173 (Forearm + Bicep)/2)) + (0.160 x gastroc) + (0.235 x thigh) + 0.432(back + chest)/2))

Body temperature (Tbody) was calculated using the equation of Baum et al. (1976)

Tbody = (0.87 x Tcore) + (0.13 x Tskin).

All temperature data for study 1 was collected continuously (1 Hz) on a personal computer using Tracer-Daq (Measurement Computing) software interfaced with an

analog to digital data acquisition board (USB Temp, Measurement Computing). For studies 2 and 3 all temperature was collected continuously (1 Hz) on a personal computer using custom software (LabView, National Instruments).

## APPENDIX C:

***Impedance Cardiography (Study 1):*** The methodology for the physioflow impedance cardiograph has been previously published by Charloux et al. (Charloux *et al.*, 2000). The methodology employed in the current study was not different than the previously described methodology, therefore the following descriptions is taken directly from Charloux et al. (Charloux *et al.*, 2000).

"Cardiac output measurement by the Physioflow device is based on the following formula;

$$Qc = fc \times SVi \times BSA$$

where Qc is cardiac output (l/min), fc is the heart rate (bpm, based on the RR interval measurement, determined on the ECG first derivative, dECG/dt, which provides more stable signal than the ECG signal itself, BSA ($m^2$) is the body surface calculated according the Hancock formula ($BSA - 0.024265 \times BM^{0.05378} \times H^{0.3964}$, where BM is body mass in kg and H is height in cm), and SVi is the SV index ($ml/min^2$; i.e. the SV divided by the BSA).

With the Physioflow device, a first evaluation of the SVi, called SVical, is computed during a calibration procedure based on 24 consecutive heart beats recorded in the resting condition. This evaluation retains the largest impedance variation during systole (Zmax – Zmin), and the largest rate of variation of the impedance signal (dZ/dtmax, called the contractility index, CTI). The SVi calculation also depends on the ventricular ejection time (t). The ventricular ejection time is usually measured using echocardiography or phonocardiography, but impedance cardiography can provide a

very precise estimation of this variable (Stern *et al.*, 1985; Mehlsen *et al.*, 1990). The designers of the Physioflow have chosen to use a related, but slightly different parameter, called the thoracic flow inversion time (TFIT, in ms). The TFIT is measured on the first mathematical derivative of the impedance signal. The TFIT is the time interval between the first zero value beginning of the cardiac cycle (beginning of the ECG's QRS) and the first nadir after the peak of the ejection velocity (dZ/dtmax). Afterwards, the TFIT is weighted [W(TFIT)] using a specific algorithm [alg(TRIT, fc, PP)] which in addition to the signal waveform, comprises two factors, the pulse pressure (PP, systolic arterial pressure – diastolic arterial pulse pressure) and fc. The impedance signal morphology is indeed affected by several phenomena that occur in the aorta. Aortic compliance contributes to the signal waveform; Chemla et al. (Chemla *et al.*, 1998) have demonstrated the existence of a linear relationship between aortic compliance and the SV/PP ration. In the [alg(TFIT, fc, PP)], the PP, calculated from sphygmomanometer measurement, is introduced at the end of the Physioflow calibration phase. Similarly, certain oscillatory and resonance phenomena in relationship with fc influence the signal morphology. Murgo et al. (Murgo *et al.*, 1980) described a relationship between pressure waveform and aortic impedance or fc, fc is second factor entering into the algorithm.

As a result of the above concepts, SVical is computed according the following formula:

$$SVical = k \times [(dZ/dtmax)/(Zmax-Zmin)] \times W(TFITcal)$$

Where k is a constant, and the subscript “cal” indicates the parameters measured during the calibration phase. SVical represents the baseline reference. During the data acquisition phase, the variations of the parameters described above are analyzed and compared to those obtained during the calibration procedure. For instance, the designers demonstrated that the SV variations result mainly from a combination of contractility fluctuations (CTI or dZ/dtmax) and of TFIT variations whereby:

$SVi = SVical \times \sqrt[3]{(CTI/CTIcal \times TFITcal/TFIT)}$.

This concept is supported by a study by Moon et al (Moon *et al.*, 1994), who showed that changes in SV, for example, during exercise, are correlated with variations in dZ/dt, but inversely correlated with variations in left ventricular ejection time. In all equations used by other impedance cardiograph devices, these two parameters appear as a product.”

# APPENDIX D

**Near infrared Spectroscopy (Study 1 and 2):** The following text is an excerpt taken from the ISS OxiplexTS operation manual describing the theory of operation and the calculations used by this NIRS system:

**"The Near Infrared Spectroscopy (NIRS) Window:**

As light passes through tissue it is both absorbed and scattered. For light with wavelengths range from 670 nm to 900 nm (near infrared region, NIR) the absorption properties of tissue are such that a measurable amount of light can pass through large volumes of tissue. Below 650 nm the absorption of hemoglobin increases to the point that no measurable light can travel through the tissue. Above 900 nm the absorption of water makes detection of light passing through tissue difficult. Thus, between 670 and 900 nm there is a unique window within which tissues can be probed by near infrared light.

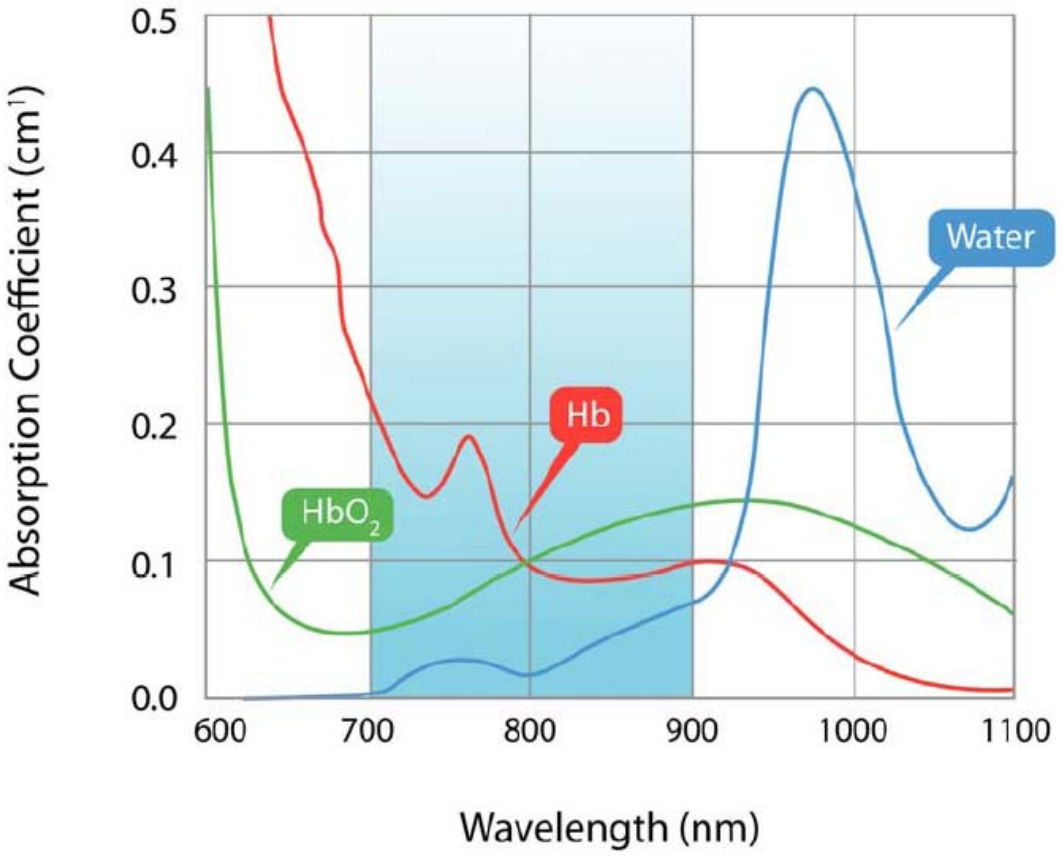


Figure 1. The absorption spectra of major absorbers (Oxygenated Hemoglobin, De-Oxygenated Hemoglobin, and Water) in the region 600-1100 nm.

**Absorption**

A *chromophore* is substance which absorbs light. In the NIR region, there are only a handful of chromophores with significant absorption. The most significant absorbers are oxygenated hemoglobin (HbO2) and de-oxygenated hemoglobin (Hb). Water is also a significant absorber followed by lipids, oxidized cytochrome oxidase (CtOx), myoglobin, melanin, and bilirubin.

The ISS OxiplexTS is designed to measure only the concentrations of oxygenated

hemoglobin (HbO2) and de-oxygenated hemoglobin (Hb). It is assumed that, during the measurement time, the water concentration is constant, and that the other chromophores are not significant absorbers in the tissue. The presence of water is accounted for by assuming a known concentration of water in the tissue. The absorption spectrum of lipids is almost the same as water and can thus be included in the water correction. The absorption spectra of myoglobin is similar to that of hemoglobin, so any significant concentrations of these chromophores will be included in the hemoglobin concentration measurements.

The light absorbing properties of a material is expressed as Absorbance (A), which is related to fraction of incident light that passes through a material by the relationship

$$A = -\log(T) \qquad [1]$$

where T is the fraction of intensity transmitted. The absorption coefficient, $U_A$ , is the absorbance per unit distance.

Assuming only the presence of hemoglobin and water, the absorption coefficient at a particular wavelength λ is given as

$$U_A = K_{HbO2}[HbO2] + K_{Hb}[Hb] + K_{H2O}[H2O] \qquad [2]$$

Where:

$U_A$ = Absorption coefficient ($cm^{-1}$)

K = Extinction coefficient ($\mu M\ M^{-1}\ cm^{-1}$)

[HbO] = concentration of oxy-hemoglobin (μM)

[Hb] = concentration of deoxy-hemoglobin (μM)

[H2O] = concentration of water (μM)

In equation [2] the extinction coefficients are known properties of the chromophores and of the water. Also, the water concentration is assumed to be 70% in tissues (the value can be changed in the Setup of OxiTS). The two unknowns are [Hb] and [HbO2].

In order to determine the concentrations of oxy- and deoxy-hemoglobin, the absorption coefficient $U_A$ is measured at two different wavelengths. The ISS OxiplexTS typically uses 690 nm and 830 nm as the measurement wavelengths.

**Scattering**

Unfortunately, the measurement of the absorption coefficient $U_A$ at a particular wavelength in tissue is complicated by the effects of scattering. Scattering occurs whenever a ray, or photon, of light crosses into a region with a different index of refraction. Or, simply, when bounces against objects that force a change in the direction of propagation. Tissues are highly inhomogeneous regions; the optical properties change on a small scale as each cell wall and tissue boundary encountered will have a different refractive index and will cause scattering. The effect of scattering is far more

significant than the effect of absorption when considering light transport through tissue in the near infrared. The scattering strength of a material at a specific wavelength is quantified using the scattering coefficient $U_S$, which like $U_A$, is measured in $cm^{-1}$.

In order to make accurate determinations of the absorption coefficient, the scattering must be accounted for. The ISS OxiplexTS measures the scattering coefficient directly and it is thus able to determine hemoglobin concentrations in any highly scattering medium.

**A Note about Absorption and Scattering Terminology**

The scattering coefficient $U_S$ referred to in this manual is actually the reduced scattering coefficient $\mu_s'$ referred to in the literature. The term "reduced" and the prime symbol have been dropped for simplicity. Also, the symbol $U_A$ is utilized in this manual and in the OxiTS software to represent the absorption coefficient, whereas the symbol $\mu_a$ is used in the literature.

**Frequency-Domain Spectroscopy**

The measurement of the absorption and of the scattering coefficients allows for OxiplexTS to provide an absolute determination of the hemoglobin concentrations in tissue. The measurement is achieved by employing the frequency-domain spectroscopy approach, which is fast and accurate. Frequency-domain spectroscopy is a technique employed for the measurement of the decay times of fluorescence. Its extension and

implementation to the studies of tissues in 1993 has allowed for the determination of the absorption and scattering coefficients in tissues.

In frequency domain spectroscopy, the light beam is modulated at a frequency *f* (the light sources used by the OxiplexTS are modulated at a frequency of 110 MHz). Mathematically, the light source intensity as a function of time is expressed as

$$I_o = I_{DCo} + I_{ACo} (\sin (2\pi ft - \Phi_o) \quad [3]$$

where:

$I_o$ = source intensity

$I_{DCo}$ = average component of the light source intensity

$I_{ACo}$ = alternating component of the light intensity

*f* = modulation frequency

$\Phi_o$ = phase of the light source

As seen in equation [3] the light source intensity is described by three parameters: the average DC component, the alternating AC component, and the Phase component. In a highly scattering media, as the light travels away from the modulated light source it spreads out in all directions. The modulated light can be described as a photon density wave traveling away from the source. In a homogeneous media the photon density wave travels at a constant speed (slower than the speed of light), and

decreases in intensity as it moves away from the source. The phase shift of the photon density wave measured at a point distant from the source is a measure of the speed of the propagation of the wave.

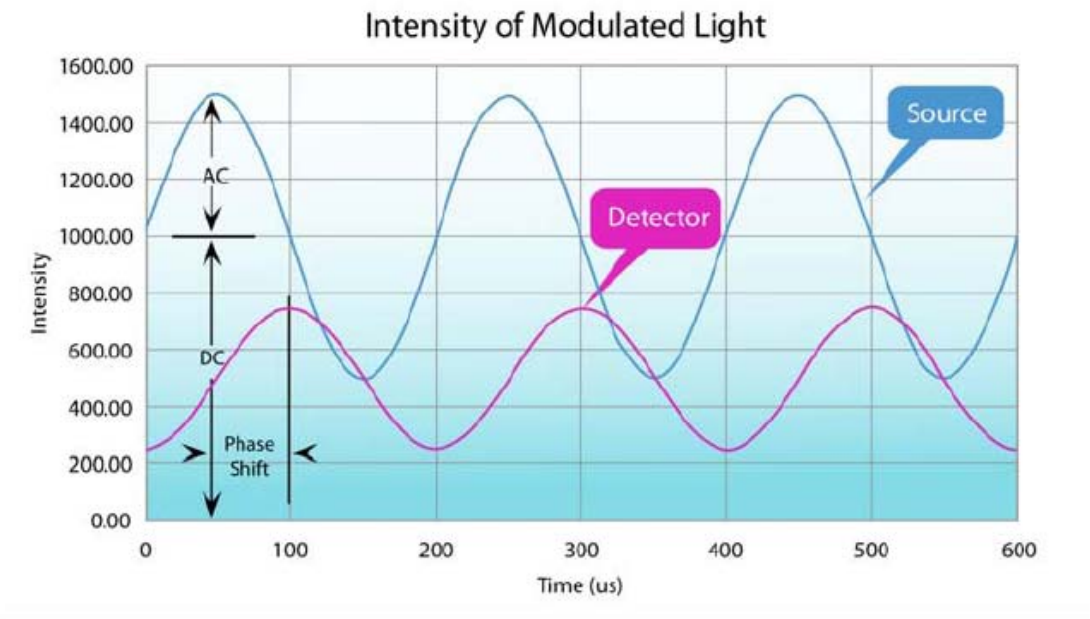


Figure 2 - The - light source modulation parameters are shown. AC is the amplitude of the modulation. DC is the average intensity. The phase shift between the two signals is also shown.

The OxiplexTS determines the absorption coefficient and the scattering coefficient of the tissue by measuring how the AC (or DC), and Phase components change as a function of distance R between the source and detector locations.

**Equations**

Assuming the sensor geometry of Figure 6.2, and the light source modulation described by Equation [3], and further assuming $U_S >> U_A$, then the propagation of the

light (photon density wave) through the tissue can be described by the following equations:

$$\ln (R^2 \bullet DC) = (R^2 \bullet S_{DC}) + K_{DC} \quad [4]$$

$$\ln (R^2 \bullet AC) = (R^2 \bullet S_{AC}) \quad [5]$$

$$(\Phi) = (R \bullet S_{\Phi}) + K_{\Phi} \quad [6]$$

On the left side of the equality of each of these equations is a value which changes linearly with the source-detector separation distance R. As the $K_n$ terms in the equations are constants, the equations describe straight lines in the form y = mx + b.

The coefficients $S_{DC}$, $S_{AC}$ and $S_{\Phi}$ are the slopes of the lines when the equations are plotted against the distance R . Moreover, the slopes are functions of $U_A$ and $U_B$, in addition to other known parameters such as modulation frequency and speed of light in the tissue.

In theory the AC, DC and phase Φ components of the signal need only be measured at two distances to determine the three slopes. However, the ISS instrument measures these values at four distances, and the “best fit” of the lines are used to determine $S_{DC}$, $S_{AC}$ and $S_{\Phi}$ using four distances instead of two improves the signal-to-noise (S/N) ratio of the measurement and its accuracy as well as the reliability performance of the device. The constants $K_n$ are arbitrary; they are not calculated since they do not affect the determination of the slopes.

Once the three slopes have been determined at a particular wavelength, $U_A$ and $U_S$ and can be calculated at that wavelength using any two of the slopes: for instance, $S_{AC}$ and $S_{\Phi}$ ,or $S_{DC}$ and $S_{\Phi}$, or $S_{AC}$ and $S_{DC}$. In practice, using $S_{AC}$ and $S_{DC}$ results in a lower S/N ratio; this couple is not utilized. The use of the pair $S_{AC}$ and $S_{\Phi}$ is preferred because the AC component of the signal is not susceptible to background light influences. When the background light is eliminated, the pair $S_{DC}$ and $S_{\Phi}$ may give a slight improvement in accuracy when the absorption properties of the calibration is very difference from the absorption of the tissue."

## APPENDIX E:

**Breath by Breath Oxygen Consumption (Study 2 and 3):** Breath by breath measurement of alveolar gas exchange was determined according to the calculations and procedures as previously described by Beaver et al. (1981). For the purpose of this study subjects breathed through a two-way non rebreathing valve connected to a pneumotachometer (Hans Rudolph, Kansas City, MO). Oxygen and carbon dioxide concentration of inspired and expired gases were determined by a mass spectrometer (Perkin-Elmer MGA 1100, St. Louis, MO). Gas samples were collected at the mouthpiece via a 6 foot capillary tube connected directly to the mass spectrometer. Custom software (Beck Integrated Physiological Systems) was used to determine breath by breath oxygen consumption. The mass spectrometer was calibrated prior to each experimental trial using gases of known concentration. Volume was calibrated using a 3 l syringe (Hans Rudolph) at low, moderate, and high flow rates.

# APPENDIX F:

***Open Circuit Acetylene Washin (Study 2 and 3).*** Cardiac output (CO) was determined by the open circuit acetylene washin technique using the iterative method (referred to as OpCirc 2 in (Johnson *et al.*, 2000) for the calculation of CO as described by Johnson et al (Johnson *et al.*, 2000). The following methodology is taken directly from Johnson et al. (Johnson *et al.*, 2000) as the technique was not modified for the present study.

Terms and Definitions:

| | |
|---|---|
| $Vti$ | Tissue volume: static volume that acetylene dissolves in |
| $\dot{Q}c$ | Pulmonary capillary blood flow |
| $V^n_{Acet}, V^n_{He}$ | Uptake volumes of acetylene and helium (ml, STPD), respectively for the *n*th breath of the washin maneuver. These are obtained by integrating the gas concentration x flow s time product for each 8-ms sample over each breath |
| $RV^n_{Acet}, RV^n_{He}$ | Residual volumes of acetylene and helium respectively for the *n*th breath |
| $F^n_{E,Acet}, F^n_{E,He}$ | End-expiratory fractional concentration of acetylene and helium respectively , for the *n*th breath |
| $F_{\bar{E},He}$ | Mixed expired fractional concentration of helium,obtained by integrating helium concentration and expiratory flow |
| $F^n_{A,Acet}, F^n_{A,He}$ | Fractional concentrations of alveolar gas for acetylene and helium, respectively. In practice, alveolar gas concentrations were obtained from end-expiratory results |
| $PB$ | Barometric pressure (mmHg) |
| $\alpha_{t,Acet}, \alpha_{b,Acet}$ | Tissue and blood solubilities of acetylene, respectively. Although these tow terms were carried through the derivation, in practice the same value, 0.74 ml•ml•tissue$^{-1}$•atm$^{-1}$, was used for both |
| $T^n_I, T^n_E$ | Inspiratory and expiratory times, respectively, of the *n*th breath |
| $VSD, V_{D,vlv}$ | Volume of serial dead space and volume of the breathing valve (ml) |
| $VA$ | Alveolar volume |

"For the calculation of cardiac output using the iterative method the lungs are considered to be one well-mixed alveolar compartment separated from the inhaled gas bag by an anatomic dead space. Gas transport in each unit of time, Δ*t* (the 8-ms sampling period of the data), is governed by the following mass balance considerations at the alveolar level.

The total acetylene volume in the alveolar compartment is given by $V_{Acet} = F_{A,Acet}$ x ($V_A + \alpha_{t,Acet}$ x Vti). The change in the acetylene volume per unit time is equal to the rate of disappearance into the blood plus the amount entering the alveolar volume by inspiring via the anatomic dead space

Equation 1:

$$V_{Acet} = F_{A,Acet} \times (V_A + \alpha_{t,Acet} \times Vti).$$

$$\frac{d[(V_A + \alpha_{t,Acet} \cdot Vti) \cdot F_{A,Acet}(t)]}{dt} = -\alpha_{t,Acet} \cdot \dot{Q} \cdot [F_{A,Acet}(t) - F_{\bar{v},Acet}] + F_{DS',Acet} \cdot \frac{dV}{dt}$$

where $F_{DS',Acet}$ indicates the fractional concentration of acetylene at the alveolar end of the dead space. This equation can be solved for $dF_{A,Acet}/dt$

Equation 2:

$$dF_{A,Acet}(t) = -\frac{dt}{V_A + \alpha_{t,Acet} \cdot Vti} \cdot \alpha_{t,Acet} \cdot \dot{Q} \cdot [F_{A,Acet}(t) - F_{\bar{v},Acet}] + \left\{ \frac{[F_{DS',Acet} - F_{A,Acet}(t)] \cdot \frac{dV}{dt} \text{ (Insp)}}{0 \text{ (Exp)}} \right\}$$

where Insp is inspiratory and Exp is expiratory.

This finite difference equation is used at each time sampling increment to update the fractional concentration of acetylene. The helium concentration is treated similarly, except that $\alpha_{t,He} = 0$ (negligible tissue solubility for helium).

The process starts with a calculation of VSD, as above, and VA, as follows

Equation 3:

$$V_A = \frac{\left[ V_I \cdot (F_I - F_E) - \sum_{k=1}^{n} (V_I^k - V_E^k) \cdot (F_E^n - F_E^{n-1}) + (V_{D,vlv} + V_{SD}) \cdot (F_E^{n-1} - F_I^n) \right]}{F_E^n - F_E^{n-1}}$$

This equation is applied to helium data for all breaths where the ratio of FE/FI is ,95% to avoid unstable solutions.

A computer algorithm then sets up a dead space volume that consists of an ordered list of 1-ml units, the total volume equaling VSD. The VA and each VSD element is initially filled with gas concentration equal to expired concentration of the breath immediately before the start of the washin maneuver, simulating end expiration. The computer then samples the first inspiratory data point, obtaining volume change, ΔV, and values for gas concentration at the mouth from the raw data stream. At the mouth end of the dead space, the first *m* = ΔV dead space elements are set to the measured gas concentration. At the alveolar end of the dead space, *m* elements are each added to the alveolar space, using *Eq.2* to update the alveolar concentration and increasing alveolar gas volume by ΔV. As the process continues during inspiration, a front of gas

moves through the dead space elements until inspired gas appears at the alveolar end of the dead space. Further inspiration adds inspired gas to the alveolar compartment. During expiration, *Eq. 2* is again applied and the dead space elements are filled from the alveolar end with the current value for alveolar gas concentration. This process continues until the entire data stream has been used, and end-tidal values for each of the breaths is obtained from the model. The sum of squared differences between measured and modeled end-tidal concentration is obtained for use in an iterative search procedure that finds the best $\dot{Q}$ and Vti.

Taylor minimization (Press, 1986) was used to find the best combination of Vti and $\dot{Q}$ that minimized the sum of squared errors between modeled and actual end-tidal gas concentrations. Imagine a three-dimensional surface shaped like a large bowl with the value for sum squared errors as the height above a plane defining the ranges of values for Vti and $\dot{Q}$. The algorithm finds the low point of this surface (bottom of bowl) by finding its local slope and descending the steepest path down the slope to the minimum. This process generally took 50–100 steps. A typical solution is shown in Fig. F.1. The solution for Vti was occasionally unphysiological, and we were unable to find methods resulting in consistently reasonable values for it. The solution for $\dot{Q}$ usually appeared reasonable despite the occasional unstable values for Vti. Thus Vti values were not reported in this study.

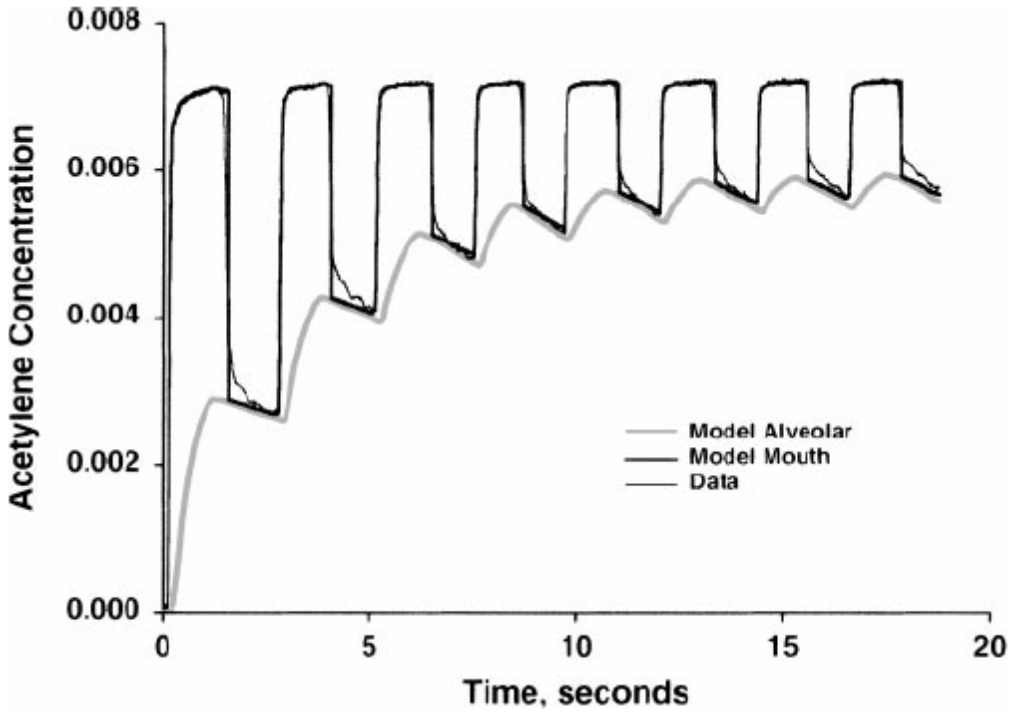


**Figure F.1.** Model demonstrating the OpCirc2 method for calculation of QT. Thin line shows raw input data for acetylene concentration at the mouth. Thick black and thick gray lines show model results for mouth and alveolar concentrations, respectively (see APPENDIX F for description of the model). In this study, the iterative methods (OpCirc2) modeled the entire alveolar gas concentration curves throughout inspiration and expiration. This is in contrast to the work of Stout et al.(Stout *et al.*, 1975) and Gan et al. (Gan *et al.*, 1993) who examined end-inspiratory and end-expiratory alveolar gas concentration and estimated the mean alveolar values.

# APPENDIX G

***Blood volume and plasma volume*:** Changes in blood and plasma volume were calculated based on the procedures described Dill and Costill (Dill & Costill, 1974). Percent changes in blood volume (BV), red cell volume (CV), and plasma volume (PV) were calculated from values of hemoglobin (Hb) and hematocrit (Hct) using the following calculations where $_B$ and $_A$ refer to before exercise and at the time point during exercise for which the change is being determined, and BVB was taken as 100:

$$BV_A = BV_B (Hb_B/Hb_A)$$

$$CV_A = BV_A (HCT_A)$$

$$PV_A = BV_A - CV_A$$

$$\Delta BV, \% = 100 (BV_A – BV_B)/ BV_B$$

$$\Delta CV, \% = 100 (CV_A – CV_B)/ CV_B$$

$$\Delta PV, \% = 100 (PV_A – PV_B)/ PV_B$$

The cyanomethemoglobin technique was used to calculate hemoglobin concentration based on the following procedure.

1. Dispense 2.0 ml of total hemoglobin reagent (Pointe Scientific, Canton, MI) into test tubes labeled; blank, low, medium, high, time 0, time 5, etc…
2. Place 0.01 ml (10µl) of standards (low = 8.1 g/dl, medium = 12.6 g/dl, high = 16.8 g/dl, supplied by manufacturer) into appropriately marked test tubes.
3. Place 0.01 ml (10µl) of fresh whole blood into appropriately labeled test tubes.

4. Allow tubes to stand for at least 3 minutes at room temperature. For this study samples were stored in a dark cabinet after collection and mixing with reagent for no longer than 7 days prior to analysis.
5. Set spectrophotometer (Beckman DU-6, Beckman Coulter) to 540 nm and zero with the reagent blank.
6. Read and record absorbance values of all tubes.
7. Create standard curve using standards provided by Pointe Scientific.

Hematocrit was determined by microcentrifugation according to the following procedure;

1. Draw whole blood by capillary action into 2 heparinized mircohematocrit tubes (Fisherbrand).
2. Fill tubes approximately 90% full.
3. Wipe excess blood from the outside of the tubes and seal one end of the tube with clay.
4. Place the tubes in the mircocentrifuge with the sealed ends against the rubber outer rim.
5. Centrifuge for 15 minute at room temperature
6. Read the red cells and total blood volume with a ruler under a microscope and calculate % of red blood cell to total.

# APPENDIX H

***Inertial load calculations: From Martin et al. (Martin et al., 1997)***

***Angular Velocity:*** Determined from the time difference between consecutive edges of slot on the target disk ($\omega = \Delta\theta/\Delta t$ where $\Delta\theta$ = angle between target disk slots in radians and $\Delta t$ = time between target disk slots in seconds).

***Instantaneous Torque (Ti):*** Calculated as the angular force applied to the cranks, calculated every 3° of crank rotation as $Ti = \alpha IG$, where I is the moment of inertia of the flywheel and G is the gear ratio, and $\alpha$ is the angular acceleration.

***Instantaneous Power (Pi):*** Calculated every 3° of crank rotation as $Pi = \alpha\omega I$.

***Torque over each complete crank revolution (Trev):*** Calculated as the rate of change of angular momentum ($Trev = I[\omega(i+1) - \omega i]/[t(i+1) - ti]$), where $\omega(i+1)$ and $t(i+1)$ are the angular velocity and time at the end of the crank revolution and $\omega i$ and ti are the angular velocity and time at the beginning of the crank revolution.

***Power over each complete crank revolution (Prev):*** Calculated as the rate of change in kinetic energy ($Prev = \Delta KE/\Delta t = 0.5\ I[\omega(i+1)^2 - \omega i^2]/[t(i+1) - ti]$).

***Moment of inertia of the flywheel:*** Calculated as the sum of the component parts. All the parts are cylindrical shaped and have a moment of inertia (I) of $I = m(ri^2 + ro^2)/2$ where m is the mass of the cyclinder and ri and ro are the inner and outer radii of the cylinder.

***Inertial load****:* Defined as one-half the product of the flywheel moment of inertia and the overall gear ratio squared (inertial load = $IG^2/2$).

# APPENDIX I

## Study 2: Table 2.4 Rectal vs. Esophageal Temperature

| | Rest | | | 40% | | | 50% | | | 60% | | | 70% | | | 80% | | | 90% | | | 100% | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Rectal Tcore, $^{o}$ C | 36.85 | ± | 0.19 | 37.10 | ± | 0.19* | 37.58 | ± | 0.22* | 37.78 | ± | 0.31* | 37.97 | ± | 0.29* | 38.08 | ± | 0.26 | 38.23 | ± | 0.35 | 38.32 | ± | 0.39 |
| Esophageal Tcore, $^{o}$ C | 37.24 | ± | 0.30† | 37.29 | ± | 0.26† | 37.53 | ± | 0.20* | 37.79 | ± | 0.22* | 37.99 | ± | .022* | 38.28 | ± | 0.28* | 38.30 | ± | 0.32 | 38.37 | ± | 0.28 |

Values are mean ± SD of 7 subjects. * indicates significant increase from previous value, † indicates signficant difference between measurements.

## APPENDIX J

*Individual data for study 1*

HEART RATE (bpm) - PLACEBO; DAY - 1

| TIME | 0 | 5 | 10 | 15 | 20 | 25 | 30 | 35 | 40 | 45 | 50 | 51 | 52 | 53 | 54 | 55 | 56 | 57 | 58 | 59 | 60 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| AW | 69.0 | 108.3 | 131.5 | 149.9 | 165.2 | 160.9 | 160.1 | 166.3 | 164.9 | 172.6 | 174.5 | 180.0 | 189.7 | 193.1 | 194.8 | 196.2 | 197.4 | 198.6 | 201.1 | 203.3 | 206.0 |
| BA | 62.0 | 91.6 | 102.3 | 109.8 | 119.8 | 125.0 | 128.3 | 126.9 | 134.5 | 140.7 | 140.1 | 141.4 | 147.4 | 150.0 | 151.2 | 151.3 | 147.8 | 145.8 | 146.4 | 149.1 | 153.4 |
| BM | 51.0 | 107.0 | 120.8 | 137.3 | 153.7 | 156.8 | 160.5 | 161.7 | 166.1 | 166.7 | 165.4 | 173.1 | 179.0 | 179.7 | 177.0 | 175.1 | 174.2 | 175.5 | 177.7 | 178.9 | 180.5 |
| DW | 48.0 | 119.9 | 133.7 | 143.7 | 153.4 | 155.8 | 156.0 | 156.3 | 154.2 | 156.5 | 158.3 | 163.6 | 169.8 | 171.9 | 171.6 | 172.0 | 172.1 | 173.8 | 173.3 | 175.2 | 176.6 |
| JG | 74.0 | 116.3 | 137.8 | 149.5 | 160.8 | 165.0 | 165.1 | 169.4 | 170.9 | 171.0 | 173.1 | 179.4 | 184.4 | 185.7 | 185.8 | 186.4 | 186.3 | 186.4 | 186.3 | 186.9 | 186.4 |
| JH | 69.0 | 114.0 | 124.1 | 134.5 | 150.5 | 157.0 | 158.5 | 161.6 | 164.4 | 166.6 | 168.0 | 173.0 | 181.0 | 183.5 | 185.7 | 187.0 | 189.1 | 189.0 | 190.0 | 191.9 | 194.0 |
| JW | 76.0 | 105.7 | 119.9 | 130.3 | 141.9 | 146.7 | 138.9 | 140.1 | 146.6 | 149.3 | 136.9 | 134.5 | 144.0 | 154.5 | 164.6 | 168.7 | 172.9 | 175.6 | 177.3 | 179.6 | 181.4 |
| KW | 58.0 | 100.7 | 118.8 | 133.5 | 145.1 | 148.1 | 149.6 | 152.9 | 153.6 | 155.3 | 153.2 | 162.2 | 173.2 | 180.5 | 183.5 | 185.9 | 187.5 | 189.2 | 189.9 | 190.7 | 191.6 |
| MT | 72.0 | 122.2 | 141.2 | 155.7 | 169.5 | 164.9 | 160.2 | 147.8 | 161.8 | 168.6 | 164.5 | 172.2 | 180.1 | 182.4 | 183.7 | 183.9 | 183.5 | 183.7 | 183.8 | 185.9 | 190.1 |
| NW | 65.0 | 111.9 | 126.9 | 139.1 | 152.2 | 161.4 | 165.5 | 160.2 | 164.5 | 166.5 | 167.3 | 169.2 | 174.0 | 175.8 | 178.0 | 177.6 | 177.9 | 178.5 | 180.7 | 180.4 | 182.7 |
| SD | 61.0 | 114.8 | 127.7 | 138.4 | 158.6 | 156.0 | 155.6 | 160.2 | 166.0 | 165.3 | 165.1 | 168.4 | 175.5 | 178.8 | 180.7 | 181.6 | 181.9 | 182.6 | 183.7 | 184.9 | 186.8 |
| SL | 70.2 | 122.2 | 128.3 | 142.0 | 152.8 | 152.5 | 150.9 | 152.8 | 153.8 | 157.4 | 159.2 | 164.3 | 171.7 | 175.0 | 178.1 | 180.5 | 181.5 | 180.9 | 181.1 | 180.1 | 180.7 |

HEART RATE (bpm) - POM; DAY - 1

| TIME | 0 | 5 | 10 | 15 | 20 | 25 | 30 | 35 | 40 | 45 | 50 | 51 | 52 | 53 | 54 | 55 | 56 | 57 | 58 | 59 | 60 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| AW | 81.0 | 119.2 | 139.1 | 153.5 | 174.6 | 173.7 | 174.7 | 181.6 | 179.6 | 189.2 | 188.8 | 191.4 | 196.1 | 197.8 | 196.8 | 195.1 | 195.0 | 194.3 | 194.4 | 195.1 | 196.7 |
| BA | 65.0 | 89.4 | 102.4 | 115.3 | 121.6 | 133.3 | 133.3 | 133.8 | 136.5 | 138.0 | 140.2 | 141.4 | 148.6 | 145.9 | 135.8 | 132.3 | 133.1 | 134.7 | 136.7 | 137.3 | 142.2 |
| BM | 62.0 | 108.5 | 122.7 | 139.0 | 155.2 | 162.7 | 166.9 | 169.7 | 171.9 | 175.3 | 177.1 | 181.5 | 185.6 | 185.8 | 182.3 | 178.7 | 177.0 | 178.8 | 180.5 | 181.5 | 183.2 |
| DW | 55.0 | 118.5 | 133.7 | 147.2 | 156.0 | 153.1 | 151.5 | 153.5 | 155.3 | 152.5 | 152.8 | 163.1 | 168.4 | 169.4 | 169.6 | 171.2 | 171.8 | 176.8 | 182.2 | 185.7 | 187.5 |
| JG | 57.0 | 114.3 | 129.7 | 144.1 | 157.9 | 157.2 | 158.0 | 158.7 | 159.1 | 163.5 | 166.9 | 172.6 | 177.2 | 178.7 | 179.8 | 177.4 | 180.2 | 177.3 | 177.5 | 178.6 | 182.5 |
| JH | 69.0 | 117.8 | 133.1 | 143.6 | 155.2 | 160.2 | 166.7 | 163.6 | 165.8 | 165.3 | 169.3 | 174.9 | 179.5 | 182.8 | 184.7 | 185.5 | 186.9 | 187.5 | 188.0 | 189.3 | 192.3 |
| JW | 65.0 | 98.4 | 109.4 | 117.8 | 135.2 | 132.4 | 139.6 | 144.1 | 139.8 | 148.3 | 143.3 | 151.3 | 161.7 | 164.9 | 169.0 | 171.9 | 174.8 | 177.1 | 181.3 | 185.2 | 190.7 |
| KW | 66.0 | 100.9 | 118.3 | 132.2 | 155.1 | 153.4 | 146.1 | 151.2 | 148.5 | 150.3 | 159.5 | 164.7 | 173.3 | 177.2 | 180.0 | 182.5 | 183.5 | 185.6 | 187.2 | 189.3 | 189.6 |
| MT | 70.0 | 117.9 | 133.3 | 151.9 | 165.3 | 164.9 | 165.0 | 160.8 | 161.2 | 165.3 | 167.6 | 174.6 | 182.8 | 182.2 | 180.4 | 181.6 | 180.0 | 179.9 | 181.1 | 185.4 | 188.9 |
| NW | 71.0 | 116.0 | 127.3 | 143.1 | 156.1 | 165.2 | 170.0 | 167.5 | 168.3 | 171.0 | 173.4 | 176.7 | 181.4 | 182.6 | 181.2 | 179.0 | 177.0 | 175.0 | 174.2 | 174.7 | 178.8 |
| SD | 69.0 | 119.9 | 130.5 | 145.7 | 160.7 | 160.4 | 164.3 | 164.3 | 166.8 | 169.5 | 175.5 | 179.1 | 183.4 | 184.8 | 186.3 | 187.8 | 187.9 | 189.4 | 190.0 | 191.3 | 195.0 |
| SL | 64.0 | 114.2 | 130.5 | 136.8 | 149.5 | 156.6 | 157.1 | 156.5 | 157.0 | 156.6 | 162.9 | 167.6 | 172.8 | 176.0 | 177.6 | 179.5 | 179.1 | 177.8 | 176.7 | 176.4 | 177.3 |

STROKE VOLUME (ml/beat) - PLACEBO; DAY - 1

| TIME | 0 | 5 | 10 | 15 | 20 | 25 | 30 | 35 | 40 | 45 | 50 | 51 | 52 | 53 | 54 | 55 | 56 | 57 | 58 | 59 | 60 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| AW | 66.0 | 89.7 | 91.0 | 94.1 | 97.1 | 97.5 | 97.2 | 97.5 | 96.6 | 95.6 | 93.3 | 94.2 | 90.8 | 95.6 | 94.7 | 96.4 | 95.9 | 94.7 | 97.1 | 95.8 | 98.7 |
| BA | 94.0 | 125.7 | 125.9 | 127.4 | 128.1 | 128.5 | 126.4 | 130.3 | 132.0 | 132.2 | 135.9 | 128.5 | 129.8 | 135.1 | 131.7 | 133.3 | 127.9 | 131.2 | 132.3 | 131.5 | 134.6 |
| BM | 101.0 | 123.5 | 127.2 | 135.4 | 136.5 | 132.3 | 135.5 | 135.8 | 134.8 | 132.2 | 129.2 | 133.6 | 134.1 | 134.9 | 132.8 | 135.3 | 132.5 | 134.2 | 133.7 | 135.3 | 134.3 |
| DW | 84.0 | 108.3 | 113.0 | 113.0 | 116.3 | 110.8 | 113.1 | 111.9 | 108.8 | 112.3 | 113.9 | 113.8 | 114.5 | 116.5 | 115.8 | 115.0 | 113.9 | 113.2 | 113.9 | 112.8 | 116.2 |
| JG | 92.0 | 114.2 | 113.0 | 116.9 | 118.0 | 120.1 | 130.5 | 125.1 | 130.1 | 121.4 | 122.5 | 122.5 | 122.3 | 124.4 | 116.7 | 130.3 | 124.4 | 129.5 | 122.8 | 125.6 | 126.3 |
| JH | 82.0 | 104.9 | 112.6 | 115.1 | 121.7 | 118.7 | 119.0 | 120.8 | 125.8 | 124.3 | 118.0 | 126.4 | 121.4 | 127.0 | 128.0 | 123.9 | 128.5 | 128.8 | 125.9 | 133.5 | 124.8 |
| JW | 99.0 | 132.4 | 129.6 | 133.5 | 135.4 | 141.7 | 144.3 | 143.8 | 139.0 | 140.9 | 135.3 | 152.5 | 141.9 | 149.0 | 162.7 | 160.2 | 172.1 | 168.6 | 185.9 | 182.4 | 155.2 |
| KW | 91.0 | 117.2 | 119.3 | 120.1 | 126.9 | 123.8 | 130.4 | 130.6 | 131.4 | 129.8 | 127.1 | 132.5 | 134.6 | 133.2 | 136.5 | 137.0 | 138.2 | 136.4 | 134.7 | 133.8 | 131.7 |
| MT | 97.0 | 123.3 | 127.6 | 130.8 | 132.3 | 131.1 | 133.5 | 121.2 | 130.8 | 135.1 | 132.5 | 135.1 | 135.8 | 137.1 | 136.4 | 135.9 | 135.3 | 134.5 | 133.4 | 135.4 | 133.4 |
| NW | 89.0 | 120.6 | 128.4 | 132.0 | 130.5 | 130.7 | 132.7 | 134.0 | 133.4 | 135.7 | 131.9 | 132.7 | 133.3 | 133.2 | 132.1 | 132.4 | 131.5 | 131.0 | 133.0 | 132.5 | 133.0 |
| SD | 70.0 | 98.9 | 99.8 | 102.9 | 96.3 | 99.5 | 98.8 | 99.3 | 100.4 | 103.2 | 99.8 | 103.6 | 102.5 | 104.5 | 104.7 | 106.2 | 105.9 | 106.0 | 108.2 | 107.4 | 105.9 |
| SL | 96.0 | 128.0 | 132.1 | 135.0 | 134.8 | 137.6 | 133.6 | 135.1 | 137.4 | 138.8 | 136.3 | 135.4 | 135.9 | 133.5 | 137.3 | 136.0 | 137.6 | 134.5 | 139.7 | 134.1 | 137.4 |

STROKE VOLUME (ml/beat) - POM; DAY - 1

| TIME | 0 | 5 | 10 | 15 | 20 | 25 | 30 | 35 | 40 | 45 | 50 | 51 | 52 | 53 | 54 | 55 | 56 | 57 | 58 | 59 | 60 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| AW | 68.0 | 97.1 | 96.1 | 103.0 | 106.9 | 106.0 | 102.8 | 106.1 | 105.3 | 107.2 | 103.5 | 103.6 | 106.3 | 105.0 | 106.9 | 107.2 | 104.9 | 104.0 | 104.0 | 106.1 | 107.6 |
| BA | 93.0 | 96.8 | 104.4 | 109.8 | 106.1 | 111.5 | 109.6 | 112.7 | 112.8 | 112.8 | 111.4 | 109.0 | 110.7 | 111.5 | 111.6 | 110.4 | 111.1 | 108.0 | 110.4 | 111.2 | 113.7 |
| BM | 84.0 | 107.1 | 111.2 | 113.5 | 117.2 | 117.6 | 115.9 | 117.2 | 117.6 | 116.2 | 116.4 | 120.6 | 118.9 | 121.2 | 119.8 | 117.7 | 114.7 | 119.7 | 119.1 | 119.6 | 121.9 |
| DW | 82.0 | 111.3 | 109.4 | 110.8 | 111.7 | 112.3 | 110.6 | 109.3 | 116.4 | 106.8 | 107.7 | 109.7 | 109.5 | 114.8 | 119.2 | 115.0 | 115.6 | 116.3 | 122.9 | 123.1 | 122.7 |
| JG | 97.0 | 122.3 | 124.7 | 124.9 | 128.1 | 130.3 | 127.6 | 128.4 | 130.4 | 119.6 | 126.3 | 123.5 | 123.0 | 123.9 | 125.6 | 119.7 | 125.4 | 127.3 | 129.7 | 126.1 | 123.8 |
| JH | 90.0 | 118.0 | 126.6 | 133.2 | 133.4 | 136.9 | 134.0 | 135.3 | 138.3 | 133.5 | 137.7 | 140.3 | 138.3 | 142.4 | 139.0 | 138.2 | 136.4 | 138.2 | 134.2 | 140.8 | 146.2 |
| JW | 113.0 | 153.6 | 156.3 | 155.9 | 162.5 | 153.4 | 152.9 | 162.5 | 163.2 | 162.6 | 159.3 | 157.1 | 158.2 | 156.9 | 162.1 | 163.5 | 163.6 | 161.0 | 163.6 | 164.2 | 174.6 |
| KW | 95.0 | 126.2 | 125.5 | 134.4 | 139.1 | 137.4 | 143.0 | 139.1 | 145.0 | 140.8 | 141.9 | 143.6 | 142.9 | 146.7 | 149.2 | 148.3 | 146.2 | 140.8 | 150.2 | 144.5 | 146.1 |
| MT | 95.0 | 116.8 | 117.1 | 122.5 | 125.4 | 125.8 | 123.7 | 131.0 | 128.4 | 131.7 | 125.9 | 123.9 | 131.6 | 128.5 | 130.8 | 126.2 | 133.4 | 132.3 | 129.1 | 125.1 | 127.2 |
| NW | 85.0 | 113.3 | 114.9 | 118.4 | 120.4 | 122.7 | 120.6 | 116.4 | 116.6 | 121.5 | 120.9 | 122.2 | 122.9 | 123.8 | 122.7 | 121.4 | 121.3 | 121.3 | 123.1 | 121.1 | 119.7 |
| SD | 71.0 | 94.0 | 100.0 | 96.9 | 103.5 | 101.7 | 102.8 | 101.4 | 102.9 | 101.5 | 108.1 | 100.6 | 99.8 | 99.8 | 102.5 | 107.5 | 101.7 | 101.6 | 108.6 | 108.4 | 106.8 |
| SL | 93.0 | 131.1 | 134.3 | 135.2 | 136.2 | 143.2 | 139.2 | 140.4 | 139.0 | 139.2 | 142.0 | 140.2 | 140.6 | 138.6 | 141.6 | 146.6 | 136.6 | 139.2 | 136.8 | 134.5 | 133.2 |

CARDIAC OUTPUT (l/min) - PLACEBO; DAY - 1

| TIME | 0 | 5 | 10 | 15 | 20 | 25 | 30 | 35 | 40 | 45 | 50 | 51 | 52 | 53 | 54 | 55 | 56 | 57 | 58 | 59 | 60 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| AW | 4.6 | 9.7 | 12.0 | 14.1 | 16.0 | 15.7 | 15.6 | 16.2 | 15.9 | 16.5 | 16.3 | 16.9 | 17.2 | 18.5 | 18.4 | 18.9 | 18.9 | 18.8 | 19.5 | 19.5 | 20.3 |
| BA | 5.8 | 11.5 | 12.9 | 14.0 | 15.3 | 16.1 | 16.2 | 16.5 | 17.8 | 18.6 | 19.0 | 18.2 | 19.1 | 20.3 | 19.9 | 20.2 | 18.9 | 19.1 | 19.4 | 19.6 | 20.7 |
| BM | 5.2 | 13.2 | 15.4 | 18.6 | 21.0 | 20.7 | 21.7 | 22.0 | 22.4 | 22.0 | 21.4 | 23.1 | 24.0 | 24.2 | 23.5 | 23.7 | 23.1 | 23.6 | 23.8 | 24.2 | 24.2 |
| DW | 4.1 | 13.0 | 15.1 | 16.2 | 17.8 | 17.3 | 17.6 | 17.5 | 16.8 | 17.6 | 18.0 | 18.6 | 19.4 | 20.0 | 19.9 | 19.8 | 19.6 | 19.7 | 19.7 | 19.8 | 20.5 |
| JG | 6.9 | 13.3 | 15.6 | 17.5 | 19.0 | 19.8 | 21.5 | 21.2 | 22.2 | 20.8 | 21.2 | 22.0 | 22.6 | 23.1 | 21.7 | 24.3 | 23.2 | 24.1 | 22.9 | 23.5 | 23.5 |
| JH | 6.0 | 12.0 | 14.0 | 15.5 | 18.3 | 18.6 | 18.9 | 19.5 | 20.7 | 20.7 | 19.8 | 21.9 | 22.0 | 23.3 | 23.8 | 23.2 | 24.3 | 24.3 | 23.9 | 25.6 | 24.2 |
| JW | 7.5 | 14.0 | 15.5 | 17.4 | 19.2 | 20.8 | 20.0 | 20.2 | 20.4 | 21.0 | 18.8 | 20.5 | 20.4 | 23.0 | 26.8 | 27.0 | 29.8 | 29.6 | 32.9 | 31.9 | 28.2 |
| KW | 5.3 | 11.8 | 14.2 | 16.0 | 18.4 | 18.3 | 19.5 | 20.0 | 20.2 | 20.2 | 19.5 | 21.5 | 23.3 | 24.1 | 25.0 | 25.5 | 25.9 | 25.8 | 25.6 | 25.5 | 25.2 |
| MT | 6.9 | 15.1 | 18.0 | 20.4 | 22.4 | 21.6 | 21.4 | 18.0 | 21.2 | 22.8 | 21.8 | 23.3 | 24.5 | 25.0 | 25.1 | 25.0 | 24.8 | 24.7 | 24.5 | 25.2 | 25.4 |
| NW | 5.8 | 13.5 | 16.3 | 18.4 | 19.9 | 21.1 | 22.0 | 21.5 | 22.0 | 22.6 | 22.1 | 22.4 | 23.2 | 23.4 | 23.5 | 23.5 | 23.4 | 23.4 | 24.0 | 23.9 | 24.3 |
| SD | 4.2 | 11.4 | 12.7 | 14.2 | 15.3 | 15.5 | 15.4 | 15.9 | 16.7 | 17.1 | 16.5 | 17.4 | 17.9 | 18.6 | 18.9 | 19.3 | 19.3 | 19.3 | 19.9 | 19.8 | 19.8 |
| SL | 6.8 | 15.6 | 17.0 | 19.2 | 20.6 | 21.0 | 20.2 | 20.6 | 21.1 | 21.8 | 21.7 | 22.3 | 23.3 | 23.4 | 24.5 | 24.6 | 25.0 | 24.3 | 25.3 | 24.1 | 24.8 |

CARDIAC OUTPUT (l/min) - POM; DAY - 1

| TIME | 0 | 5 | 10 | 15 | 20 | 25 | 30 | 35 | 40 | 45 | 50 | 51 | 52 | 53 | 54 | 55 | 56 | 57 | 58 | 59 | 60 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| AW | 5.5 | 11.6 | 13.4 | 15.8 | 18.7 | 18.4 | 18.0 | 19.3 | 18.9 | 20.3 | 19.5 | 19.8 | 20.9 | 20.8 | 21.0 | 20.9 | 20.4 | 20.2 | 20.2 | 20.7 | 21.2 |
| BA | 6.0 | 8.7 | 10.7 | 12.7 | 12.9 | 14.9 | 14.6 | 15.1 | 15.4 | 15.6 | 15.6 | 15.4 | 16.5 | 16.3 | 15.2 | 14.6 | 14.8 | 14.6 | 15.1 | 15.3 | 16.2 |
| BM | 5.2 | 11.6 | 13.6 | 15.8 | 18.2 | 19.1 | 19.3 | 19.9 | 20.2 | 20.4 | 20.6 | 21.9 | 22.1 | 22.5 | 21.8 | 21.0 | 20.3 | 21.4 | 21.5 | 21.7 | 22.3 |
| DW | 4.5 | 13.2 | 14.6 | 16.3 | 17.4 | 17.2 | 16.8 | 16.8 | 18.1 | 16.3 | 16.5 | 17.9 | 18.4 | 19.4 | 20.2 | 19.7 | 19.9 | 20.6 | 22.4 | 22.9 | 23.0 |
| JG | 5.5 | 14.0 | 16.2 | 18.0 | 20.2 | 20.5 | 20.2 | 20.4 | 20.7 | 19.6 | 21.1 | 21.3 | 21.8 | 22.2 | 22.6 | 21.2 | 22.6 | 22.6 | 23.0 | 22.5 | 22.6 |
| JH | 6.2 | 13.9 | 16.8 | 19.1 | 20.7 | 21.9 | 22.4 | 22.1 | 22.9 | 22.1 | 23.3 | 24.5 | 24.8 | 26.0 | 25.7 | 25.6 | 25.5 | 25.9 | 25.2 | 26.7 | 28.1 |
| JW | 7.3 | 15.1 | 17.1 | 18.4 | 22.0 | 20.3 | 21.4 | 23.4 | 22.8 | 24.1 | 22.8 | 23.8 | 25.6 | 25.9 | 27.4 | 28.1 | 28.6 | 28.5 | 29.7 | 30.4 | 32.1 |
| KW | 6.3 | 12.7 | 14.8 | 17.8 | 21.6 | 21.1 | 20.9 | 21.0 | 21.5 | 21.2 | 22.6 | 23.7 | 24.8 | 26.0 | 26.8 | 27.1 | 26.8 | 26.1 | 28.1 | 27.4 | 27.7 |
| MT | 6.7 | 13.8 | 15.6 | 18.6 | 20.7 | 20.7 | 20.4 | 21.1 | 20.7 | 21.8 | 21.1 | 21.6 | 24.1 | 23.4 | 23.6 | 22.9 | 24.0 | 23.8 | 23.4 | 23.2 | 24.0 |
| NW | 6.1 | 13.1 | 14.6 | 16.9 | 18.8 | 20.3 | 20.5 | 19.5 | 19.6 | 20.8 | 21.0 | 21.6 | 22.3 | 22.6 | 22.2 | 21.7 | 21.5 | 21.2 | 21.4 | 21.2 | 21.4 |
| SD | 4.9 | 11.3 | 13.0 | 14.1 | 16.6 | 16.3 | 16.9 | 16.7 | 17.2 | 17.2 | 19.0 | 18.0 | 18.3 | 18.4 | 19.1 | 20.2 | 19.1 | 19.3 | 20.6 | 20.7 | 20.8 |
| SL | 6.0 | 15.0 | 17.5 | 18.5 | 20.4 | 22.4 | 21.9 | 22.0 | 21.8 | 21.8 | 23.1 | 23.5 | 24.3 | 24.4 | 25.1 | 26.3 | 24.5 | 24.7 | 24.2 | 23.7 | 23.6 |

SYSTOLIC BLOOD PRESSURE (mmHg) - PLACEBO; DAY - 1

| TIME | 0 | 5 | 10 | 15 | 20 | 30 | 45 | 50 | 52 | 54 | 56 | 58 | 60 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| AW | 114 | 152 | 161 | 171 | 186 | 176 | 183 | 176 | 191 | 192 | 193 | 203 | 194 |
| BA | 124 | 166 | 173 | 181 | 187 | 190 | 188 | 188 | 202 | 207 | 200 | 194 | 203 |
| BM | 129 | 173 | 195 | 206 | 227 | 236 | 230 | 223 | 232 | 230 | 210 | 224 | 220 |
| DW | 120 | 163 | 171 | 175 | 191 | 185 | 187 | 189 | 211 | 197 | 192 | 188 | 202 |
| JG | 126 | 180 | 206 | 217 | 205 | 212 | 221 | 214 | 230 | 262 | 206 | 246 | 222 |
| JH | 126 | 126 | 148 | 163 | 172 | 186 | 173 | 178 | 193 | 210 | 188 | 204 | 199 |
| JW | 122 | 169 | 175 | 174 | 191 | 190 | 188 | 186 | 203 | 217 | 246 | 253 | 223 |
| KW | 112 | 159 | 171 | 170 | 172 | 187 | 178 | 177 | 190 | 203 | 196 | 196 | 173 |
| MT | 131 | 143 | 162 | 172 | 187 | 196 | 177 | 189 | 198 | 202 | 202 | 206 | 213 |
| NW | 119 | 129 | 177 | 178 | 193 | 195 | 180 | 184 | 194 | 185 | 176 | 180 | 183 |
| SD | 126 | 173 | 184 | 193 | 215 | 204 | 201 | 188 | 205 | 210 | 214 | 219 | 224 |
| SL | 120 | 168 | 163 | 180 | 191 | 192 | 204 | 208 | 217 | 221 | 222 | 225 | 214 |

SYSTOLIC BLOOD PRESSURE (mmHg) - POMS; DAY - 1

| TIME | 0 | 5 | 10 | 15 | 20 | 30 | 45 | 50 | 52 | 54 | 56 | 58 | 60 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| AW | 126 | 178 | 191 | 169 | 184 | 176 | 165 | 159 | 177 | 184 | 186 | 170 | 169 |
| BA | 128 | 157 | 178 | 169 | 186 | 195 | 189 | 194 | 204 | 209 | 194 | 203 | 206 |
| BM | 123 | 123 | 194 | 203 | 225 | 210 | 212 | 207 | 207 | 198 | 197 | 200 | 199 |
| DW | 124 | 154 | 174 | 191 | 196 | 186 | 194 | 225 | 207 | 202 | 207 | 187 | 216 |
| JG | 128 | 170 | 193 | 211 | 213 | 210 | 203 | 217 | 224 | 205 | 221 | 211 | 208 |
| JH | 119 | 137 | 147 | 158 | 187 | 191 | 184 | 185 | 197 | 213 | 207 | 216 | 202 |
| JW | 135 | 160 | 169 | 182 | 192 | 192 | 186 | 197 | 191 | 209 | 202 | 238 | 243 |
| KW | 123 | 145 | 162 | 164 | 174 | 170 | 171 | 163 | 178 | 200 | 197 | 193 | 202 |
| MT | 126 | 165 | 167 | 177 | 191 | 156 | 177 | 181 | 184 | 182 | 187 | 193 | 188 |
| NW | 115 | 157 | 168 | 169 | 197 | 194 | 182 | 177 | 178 | 182 | 178 | 164 | 174 |
| SD | 129 | 184 | 195 | 204 | 212 | 210 | 203 | 202 | 207 | 216 | 222 | 216 | 222 |
| SL | 132 | 159 | 172 | 184 | 208 | 198 | 197 | 192 | 206 | 210 | 212 | 198 | 208 |

DIASTOLIC BLOOD PRESSURE (mmHg) - PLACEBO; DAY - 1

| TIME | 0 | 5 | 10 | 15 | 20 | 30 | 45 | 50 | 52 | 54 | 56 | 58 | 60 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| AW | 92 | 86 | 95 | 86 | 84 | 66 | 69 | 57 | 88 | 95 | 86 | 89 | 76 |
| BA | 87 | 84 | 79 | 82 | 78 | 73 | 79 | 80 | 78 | 82 | 84 | 83 | 64 |
| BM | 85 | 70 | 82 | 71 | 67 | 85 | 70 | 80 | 71 | 73 | 76 | 75 | 71 |
| DW | 82 | 81 | 78 | 61 | 59 | 71 | 72 | 80 | 81 | 75 | 67 | 86 | 82 |
| JG | 72 | 80 | 79 | 80 | 79 | 83 | 77 | 69 | 69 | 77 | 47 | 43 | 53 |
| JH | 84 | 81 | 78 | 62 | 70 | 70 | 66 | 79 | 69 | 76 | 72 | 77 | 82 |
| JW | 85 | 100 | 86 | 84 | 78 | 73 | 77 | 76 | 67 | 97 | 74 | 96 | 70 |
| KW | 71 | 100 | 76 | 81 | 86 | 89 | 89 | 90 | 93 | 88 | 81 | 83 | 80 |
| MT | 89 | 63 | 59 | 52 | 46 | 53 | 69 | 60 | 80 | 74 | 72 | 69 | 74 |
| NW | 89 | 89 | 87 | 83 | 75 | 76 | 76 | 72 | 67 | 68 | 71 | 68 | 64 |
| SD | 78 | 95 | 87 | 83 | 79 | 85 | 84 | 88 | 94 | 91 | 91 | 87 | 98 |
| SL | 82 | 58 | 55 | 56 | 54 | 57 | 54 | 64 | 68 | 62 | 65 | 67 | 48 |

DIASTOLIC BLOOD PRESSURE (mmHg) - POMS; DAY - 1

| TIME | 0 | 5 | 10 | 15 | 20 | 30 | 45 | 50 | 52 | 54 | 56 | 58 | 60 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| AW | 97 | 93 | 82 | 71 | 70 | 81 | 109 | 107 | 97 | 96 | 92 | 76 | 82 |
| BA | 90 | 76 | 83 | 73 | 73 | 77 | 79 | 78 | 63 | 86 | 80 | 87 | 84 |
| BM | 88 | 83 | 80 | 85 | 78 | 79 | 80 | 82 | 73 | 69 | 81 | 66 | 65 |
| DW | 86 | 76 | 75 | 80 | 74 | 84 | 80 | 79 | 69 | 90 | 86 | 84 | 82 |
| JG | 64 | 64 | 63 | 74 | 55 | 63 | 65 | 81 | 68 | 75 | 80 | 74 | 81 |
| JH | 81 | 74 | 60 | 63 | 61 | 69 | 63 | 68 | 63 | 70 | 63 | 75 | 69 |
| JW | 86 | 97 | 71 | 76 | 84 | 77 | 71 | 78 | 84 | 76 | 78 | 88 | 91 |
| KW | 81 | 71 | 91 | 86 | 80 | 76 | 76 | 74 | 79 | 79 | 86 | 73 | 75 |
| MT | 80 | 62 | 62 | 56 | 61 | 67 | 62 | 53 | 53 | 52 | 56 | 53 | 87 |
| NW | 80 | 85 | 85 | 79 | 75 | 81 | 70 | 80 | 63 | 69 | 78 | 69 | 75 |
| SD | 94 | 99 | 98 | 84 | 87 | 83 | 85 | 98 | 94 | 96 | 96 | 88 | 94 |
| SL | 90 | 84 | 67 | 59 | 53 | 54 | 56 | 57 | 66 | 59 | 66 | 57 | 56 |

MEAN ARTERIAL BLOOD PRESSURE (mmHg) - PLACEBO; DAY - 1

| TIME | 0 | 5 | 10 | 15 | 20 | 30 | 45 | 50 | 52 | 54 | 56 | 58 | 60 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| AW | 99 | 108 | 117 | 114 | 118 | 103 | 107 | 97 | 122 | 127 | 122 | 127 | 115 |
| BA | 99 | 111 | 110 | 115 | 114 | 112 | 115 | 116 | 119 | 124 | 123 | 120 | 110 |
| BM | 100 | 104 | 120 | 116 | 120 | 135 | 123 | 128 | 125 | 125 | 121 | 125 | 121 |
| DW | 95 | 108 | 109 | 99 | 103 | 109 | 110 | 116 | 124 | 116 | 109 | 120 | 122 |
| JG | 90 | 113 | 121 | 126 | 121 | 126 | 125 | 117 | 123 | 139 | 100 | 111 | 109 |
| JH | 98 | 96 | 101 | 96 | 104 | 109 | 102 | 112 | 110 | 121 | 111 | 119 | 121 |
| JW | 97 | 123 | 116 | 114 | 116 | 112 | 114 | 113 | 112 | 137 | 131 | 148 | 121 |
| KW | 85 | 120 | 108 | 111 | 115 | 122 | 119 | 119 | 126 | 126 | 120 | 121 | 111 |
| MT | 103 | 90 | 93 | 92 | 93 | 101 | 105 | 103 | 119 | 117 | 115 | 115 | 120 |
| NW | 99 | 102 | 117 | 115 | 114 | 116 | 111 | 109 | 109 | 107 | 106 | 105 | 104 |
| SD | 94 | 121 | 119 | 120 | 124 | 125 | 123 | 121 | 131 | 131 | 132 | 131 | 140 |
| SL | 95 | 95 | 91 | 97 | 100 | 102 | 104 | 112 | 118 | 115 | 117 | 120 | 103 |

MEAN ARTERIAL BLOOD PRESSURE (mmHg) - POMS; DAY - 1

| TIME | 0 | 5 | 10 | 15 | 20 | 30 | 45 | 50 | 52 | 54 | 56 | 58 | 60 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| AW | 107 | 121 | 118 | 104 | 108 | 113 | 128 | 124 | 124 | 125 | 123 | 107 | 111 |
| BA | 103 | 103 | 115 | 105 | 111 | 116 | 116 | 117 | 110 | 127 | 118 | 126 | 125 |
| BM | 100 | 96 | 118 | 124 | 127 | 123 | 124 | 124 | 118 | 112 | 120 | 111 | 110 |
| DW | 99 | 102 | 108 | 117 | 115 | 118 | 118 | 128 | 115 | 127 | 126 | 118 | 127 |
| JG | 85 | 99 | 106 | 120 | 108 | 112 | 111 | 126 | 120 | 118 | 127 | 120 | 123 |
| JH | 94 | 95 | 89 | 95 | 103 | 110 | 103 | 107 | 108 | 118 | 111 | 122 | 113 |
| JW | 102 | 118 | 104 | 111 | 120 | 115 | 109 | 118 | 120 | 120 | 119 | 138 | 141 |
| KW | 95 | 96 | 115 | 112 | 111 | 107 | 108 | 104 | 112 | 119 | 123 | 113 | 117 |
| MT | 95 | 96 | 97 | 96 | 104 | 97 | 100 | 96 | 97 | 95 | 100 | 100 | 121 |
| NW | 92 | 109 | 113 | 109 | 116 | 119 | 107 | 112 | 101 | 106 | 111 | 101 | 108 |
| SD | 106 | 127 | 130 | 124 | 129 | 125 | 124 | 133 | 132 | 136 | 138 | 131 | 137 |
| SL | 104 | 109 | 102 | 101 | 105 | 102 | 103 | 102 | 113 | 109 | 115 | 104 | 107 |

| | VENTILATION (l/min) - PLACEBO; DAY - 1 | | | |
|---|---|---|---|---|
| TIME | 5 | 10 | 15 | 20 |
| AW | 35 | 45 | 56 | 68 |
| BA | 37 | 43 | 52 | 62 |
| BM | 35 | 45 | 55 | 67 |
| DW | 39 | 50 | 57 | 69 |
| JG | 39 | 52 | 58 | 69 |
| JH | 29 | 37 | 43 | 51 |
| JW | 35 | 48 | 55 | 67 |
| KW | 36 | 55 | 62 | 73 |
| MT | 29 | 41 | 49 | 63 |
| NW | 35 | 47 | 57 | 66 |
| SD | 41 | 54 | 62 | 78 |
| SL | 38 | 46 | 56 | 70 |

| | VENTILATION (l/min) - POMS; DAY - 1 | | | |
|---|---|---|---|---|
| TIME | 5 | 10 | 15 | 20 |
| AW | 36 | 47 | 54 | 69 |
| BA | 34 | 47 | 54 | 62 |
| BM | 34 | 44 | 54 | 69 |
| DW | 43 | 50 | 62 | 73 |
| JG | 38 | 46 | 58 | 69 |
| JH | 29 | 34 | 44 | 52 |
| JW | 34 | 43 | 50 | 65 |
| KW | 39 | 52 | 65 | 84 |
| MT | 33 | 41 | 53 | 66 |
| NW | 39 | 49 | 59 | 70 |
| SD | 43 | 52 | 65 | 78 |
| SL | 38 | 48 | 54 | 68 |

| | OXYGEN CONSUMPTIONS (l/min) - PLACEBO; | | | |
|---|---|---|---|---|
| TIME | 5 | 10 | 15 | 20 |
| AW | 1790 | 2332 | 2836 | 3346 |
| BA | 1852 | 2267 | 2688 | 3199 |
| BM | 1664 | 2111 | 2587 | 3036 |
| DW | 1915 | 2389 | 2727 | 3208 |
| JG | 1909 | 2502 | 2804 | 3266 |
| JH | 1677 | 2098 | 2454 | 3061 |
| JW | 1741 | 2436 | 2761 | 3199 |
| KW | 1932 | 2891 | 3225 | 3724 |
| MT | 1531 | 2059 | 2468 | 2960 |
| NW | 1789 | 2342 | 2818 | 3314 |
| SD | 2090 | 2590 | 3042 | 3623 |
| SL | 1795 | 2150 | 2708 | 3319 |

| | OXYGEN CONSUMPTION (l/min) - POMS; DAY | | | |
|---|---|---|---|---|
| TIME | 5 | 10 | 15 | 20 |
| AW | 1895 | 2394 | 2857 | 3332 |
| BA | 1761 | 2440 | 2706 | 3260 |
| BM | 1713 | 2199 | 2611 | 3119 |
| DW | 2044 | 2456 | 3032 | 3592 |
| JG | 1958 | 2301 | 2826 | 3294 |
| JH | 1704 | 2148 | 2607 | 3012 |
| JW | 1738 | 2172 | 2670 | 3162 |
| KW | 1938 | 2671 | 3261 | 3981 |
| MT | 1650 | 2016 | 2561 | 2966 |
| NW | 2103 | 2457 | 3066 | 3424 |
| SD | 2180 | 2585 | 3154 | 3558 |
| SL | 1905 | 2409 | 2721 | 3184 |

| | RESPIRATORY EXCHANGE RATIO - PLACEBO; D | | | |
|---|---|---|---|---|
| TIME | 5 | 10 | 15 | 20 |
| AW | 0.87 | 0.90 | 0.89 | 0.91 |
| BA | 0.84 | 0.83 | 0.84 | 0.84 |
| BM | 0.86 | 0.88 | 0.88 | 0.90 |
| DW | 0.81 | 0.83 | 0.86 | 0.87 |
| JG | 0.84 | 0.86 | 0.86 | 0.87 |
| JH | 0.83 | 0.89 | 0.89 | 0.89 |
| JW | 0.87 | 0.91 | 0.90 | 0.93 |
| KW | 0.81 | 0.85 | 0.86 | 0.84 |
| MT | 0.90 | 0.93 | 0.94 | 0.97 |
| NW | 0.80 | 0.82 | 0.82 | 0.84 |
| SD | 0.81 | 0.84 | 0.83 | 0.87 |
| SL | 0.87 | 0.89 | 0.89 | 0.89 |

| | RESPIRATORY EXCHANGE RATIO - POMS; DAY | | | |
|---|---|---|---|---|
| TIME | 5 | 10 | 15 | 20 |
| AW | 0.84 | 0.89 | 0.89 | 0.92 |
| BA | 0.82 | 0.85 | 0.86 | 0.83 |
| BM | 0.84 | 0.87 | 0.88 | 0.90 |
| DW | 0.84 | 0.83 | 0.84 | 0.85 |
| JG | 0.82 | 0.86 | 0.86 | 0.86 |
| JH | 0.79 | 0.82 | 0.84 | 0.86 |
| JW | 0.86 | 0.89 | 0.89 | 0.91 |
| KW | 0.86 | 0.86 | 0.87 | 0.89 |
| MT | 0.91 | 0.92 | 0.96 | 0.97 |
| NW | 0.83 | 0.85 | 0.85 | 0.88 |
| SD | 0.84 | 0.84 | 0.85 | 0.88 |
| SL | 0.83 | 0.83 | 0.84 | 0.87 |

| | GROSS EFFICIECNY (%) - PLACEBO; DAY - 1 | | | |
|---|---|---|---|---|
| TIME | 5 | 10 | 15 | 20 |
| AW | 18.2% | 20.6% | 21.8% | 22.1% |
| BA | 13.9% | 17.8% | 20.2% | 21.4% |
| BM | 17.7% | 20.1% | 21.4% | 22.3% |
| DW | 16.8% | 18.6% | 20.7% | 21.4% |
| JG | 18.3% | 18.2% | 20.1% | 20.6% |
| JH | 15.0% | 17.1% | 19.1% | 19.1% |
| JW | 15.3% | 16.1% | 18.8% | 20.0% |
| KW | 14.9% | 16.0% | 19.8% | 22.0% |
| MT | 17.5% | 19.1% | 21.0% | 21.6% |
| NW | 14.8% | 17.6% | 19.9% | 21.4% |
| SD | 16.2% | 17.7% | 19.2% | 19.3% |
| SL | 15.8% | 18.6% | 19.1% | 19.2% |

| | GROSS EFFICIENCY (%) - POMS; DAY - 1 | | | |
|---|---|---|---|---|
| TIME | 5 | 10 | 15 | 20 |
| AW | 17.3% | 20.1% | 21.7% | 22.2% |
| BA | 14.7% | 16.4% | 19.9% | 21.1% |
| BM | 17.2% | 19.3% | 21.2% | 21.7% |
| DW | 15.6% | 18.1% | 18.7% | 19.2% |
| JG | 17.9% | 19.8% | 20.0% | 20.4% |
| JH | 14.9% | 17.0% | 18.2% | 19.5% |
| JW | 15.4% | 18.1% | 19.5% | 20.4% |
| KW | 14.7% | 17.3% | 19.5% | 20.3% |
| MT | 16.2% | 19.5% | 20.2% | 21.6% |
| NW | 12.5% | 16.7% | 18.2% | 20.5% |
| SD | 15.5% | 17.7% | 18.4% | 19.6% |
| SL | 15.1% | 16.8% | 19.2% | 20.1% |

CORE TEMPERATURE (ºC) - PLACEBO; DAY - 1

| TIME | 0 | 5 | 10 | 15 | 20 | 25 | 30 | 35 | 40 | 45 | 50 | 51 | 52 | 53 | 54 | 55 | 56 | 57 | 58 | 59 | 60 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| AW | 37.17 | 37.21 | 37.30 | 37.43 | 37.61 | 37.75 | 37.85 | 37.93 | 38.02 | 38.07 | 38.15 | 38.16 | 38.19 | 38.22 | 38.25 | 38.29 | 38.33 | 38.38 | 38.42 | 38.43 | 38.45 |
| BA | 37.67 | 37.80 | 37.92 | 38.04 | 38.18 | 38.32 | 38.41 | 38.27 | 38.41 | 38.50 | 38.58 | 38.59 | 38.61 | 38.64 | 38.67 | 38.70 | 38.72 | 38.75 | 38.77 | 38.79 | 38.81 |
| BM | 36.88 | 36.98 | 37.25 | 37.49 | 37.76 | 37.99 | 38.17 | 38.30 | 38.38 | 38.47 | 38.53 | 38.54 | 38.56 | 38.61 | 38.67 | 38.73 | 38.78 | 38.83 | 38.85 | 38.87 | 38.90 |
| DW | 36.94 | 37.01 | 37.28 | 37.57 | 37.82 | 38.04 | 38.15 | 38.24 | 38.30 | 38.33 | 38.29 | 38.29 | 38.30 | 38.33 | 38.37 | 38.42 | 38.47 | 38.52 | 38.56 | 38.60 | 38.64 |
| JG | 37.28 | 37.41 | 37.61 | 37.82 | 38.07 | 38.33 | 38.52 | 38.65 | 38.75 | 38.81 | 38.86 | 38.87 | 38.90 | 38.93 | 38.98 | 39.03 | 39.09 | 39.16 | 39.22 | 39.30 | 39.38 |
| JH | 37.25 | 37.30 | 37.46 | 37.68 | 37.94 | 38.19 | 38.41 | 38.55 | 38.66 | 38.75 | 38.81 | 38.82 | 38.84 | 38.89 | 38.94 | 39.01 | 39.09 | 39.18 | 39.26 | 39.35 | 39.44 |
| JW | 37.61 | 37.62 | 37.67 | 37.74 | 37.84 | 37.97 | 38.07 | 38.12 | 38.14 | 38.20 | 38.16 | 38.16 | 38.17 | 38.19 | 38.22 | 38.27 | 38.32 | 38.38 | 38.45 | 38.52 | 38.60 |
| KW | 37.12 | 37.14 | 37.24 | 37.38 | 37.56 | 37.78 | 37.95 | 38.11 | 38.26 | 38.38 | 38.46 | 38.47 | 38.50 | 38.54 | 38.59 | 38.66 | 38.72 | 38.79 | 38.86 | 38.94 | 39.02 |
| MT | 37.81 | 37.94 | 37.97 | 38.10 | 38.28 | 38.45 | 38.57 | 38.65 | 38.78 | 38.83 | 38.86 | 38.87 | 38.89 | 38.92 | 38.96 | 39.00 | 39.04 | 39.07 | 39.10 | 39.13 | 39.16 |
| NW | 37.33 | 37.40 | 37.44 | 37.53 | 37.68 | 37.90 | 38.15 | 38.34 | 38.44 | 38.49 | 38.54 | 38.55 | 38.56 | 38.58 | 38.62 | 38.66 | 38.70 | 38.75 | 38.79 | 38.83 | 38.88 |
| SD | 36.99 | 37.00 | 37.15 | 37.29 | 37.47 | 37.64 | 37.75 | 37.82 | 37.87 | 37.97 | 38.02 | 38.02 | 38.06 | 38.11 | 38.16 | 38.21 | 38.25 | 38.29 | 38.32 | 38.35 | 38.38 |
| SL | 37.53 | 37.59 | 37.69 | 37.81 | 37.94 | 38.15 | 38.23 | 38.30 | 38.39 | 38.45 | 38.56 | 38.62 | 38.69 | 38.76 | 38.85 | 38.93 | 39.03 | 39.03 | 39.07 | 39.11 | 39.16 |

CORE TEMPERATURE (ºC) - POMS; DAY - 1

| TIME | 0 | 5 | 10 | 15 | 20 | 25 | 30 | 35 | 40 | 45 | 50 | 51 | 52 | 53 | 54 | 55 | 56 | 57 | 58 | 59 | 60 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| AW | 37.24 | 37.25 | 37.34 | 37.46 | 37.63 | 37.80 | 37.93 | 38.04 | 38.14 | 38.25 | 38.36 | 38.37 | 38.39 | 38.42 | 38.44 | 38.47 | 38.49 | 38.52 | 38.55 | 38.57 | 38.60 |
| BA | 37.53 | 37.51 | 37.62 | 37.81 | 37.99 | 38.15 | 38.32 | 38.43 | 38.48 | 38.48 | 38.49 | 38.49 | 38.50 | 38.51 | 38.52 | 38.51 | 38.48 | 38.46 | 38.45 | 38.45 | 38.45 |
| BM | 37.16 | 37.25 | 37.51 | 37.78 | 38.05 | 38.31 | 38.53 | 38.72 | 38.82 | 38.97 | 39.05 | 39.09 | 39.15 | 39.19 | 39.24 | 39.28 | 39.32 | 39.34 | 39.38 | 39.41 | 39.42 |
| DW | 36.97 | 37.05 | 37.26 | 37.54 | 37.76 | 37.91 | 38.03 | 38.10 | 38.11 | 38.19 | 38.26 | 38.27 | 38.27 | 38.29 | 38.32 | 38.34 | 38.40 | 38.47 | 38.55 | 38.63 | 38.73 |
| JG | 37.08 | 37.17 | 37.34 | 37.52 | 37.79 | 38.06 | 38.24 | 38.38 | 38.46 | 38.50 | 38.58 | 38.59 | 38.61 | 38.66 | 38.71 | 38.77 | 38.83 | 38.89 | 38.94 | 38.99 | 39.04 |
| JH | 37.07 | 37.10 | 37.25 | 37.43 | 37.62 | 37.87 | 38.12 | 38.29 | 38.40 | 38.48 | 38.56 | 38.58 | 38.60 | 38.65 | 38.71 | 38.79 | 38.87 | 38.95 | 39.03 | 39.11 | 39.20 |
| JW | 37.49 | 37.58 | 37.71 | 37.77 | 37.88 | 37.90 | 38.04 | 38.15 | 38.25 | 38.30 | 38.37 | 38.38 | 38.42 | 38.48 | 38.54 | 38.61 | 38.67 | 38.73 | 38.80 | 38.88 | 38.97 |
| KW | 37.13 | 37.18 | 37.25 | 37.33 | 37.43 | 37.60 | 37.75 | 37.95 | 38.08 | 38.22 | 38.28 | 38.28 | 38.33 | 38.36 | 38.40 | 38.44 | 38.48 | 38.52 | 38.55 | 38.58 | 38.63 |
| MT | 37.59 | 37.66 | 37.80 | 37.99 | 38.18 | 38.34 | 38.44 | 38.53 | 38.60 | 38.66 | 38.82 | 38.85 | 38.88 | 38.90 | 38.93 | 38.96 | 38.99 | 38.96 | 38.82 | 38.80 | 38.85 |
| NW | 37.55 | 37.51 | 37.55 | 37.68 | 37.86 | 38.10 | 38.33 | 38.41 | 38.53 | 38.76 | 38.85 | 38.89 | 38.94 | 38.96 | 38.98 | 38.99 | 39.01 | 39.03 | 39.02 | 38.90 | 38.86 |
| SD | 37.08 | 37.09 | 37.18 | 37.30 | 37.46 | 37.63 | 37.76 | 37.87 | 37.98 | 38.06 | 38.15 | 38.17 | 38.21 | 38.24 | 38.29 | 38.35 | 38.42 | 38.48 | 38.55 | 38.62 | 38.68 |
| SL | 37.31 | 37.35 | 37.49 | 37.64 | 37.81 | 38.00 | 38.20 | 38.35 | 38.48 | 38.60 | 38.64 | 38.65 | 38.66 | 38.69 | 38.72 | 38.77 | 38.82 | 38.88 | 38.94 | 39.00 | 39.06 |

SKIN TEMPERATURE (ºC) - PLACEBO; DAY - 1

| TIME | 0 | 5 | 10 | 15 | 20 | 25 | 30 | 35 | 40 | 45 | 50 | 51 | 52 | 53 | 54 | 55 | 56 | 57 | 58 | 59 | 60 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| AW | 31.42 | 31.52 | 31.41 | 31.57 | 30.90 | 30.60 | 30.54 | 30.17 | 30.01 | 30.84 | 30.46 | 30.30 | 30.28 | 30.31 | 30.23 | 30.00 | 29.86 | 29.81 | 29.87 | 29.88 | 29.79 |
| BA | 29.69 | 32.54 | 32.62 | 32.46 | 32.53 | 32.05 | 31.69 | 31.90 | 31.97 | 31.11 | 31.19 | 31.32 | 31.45 | 31.42 | 31.29 | 31.18 | 31.08 | 30.98 | 30.97 | 30.94 | 30.87 |
| BM | 32.20 | 31.84 | 31.40 | 31.96 | 31.67 | 31.83 | 31.47 | 31.65 | 31.86 | 30.25 | 29.91 | 29.83 | 30.19 | 30.15 | 30.09 | 30.15 | 30.23 | 30.30 | 30.77 | 30.98 | 30.60 |
| DW | 33.16 | 32.70 | 32.00 | 32.67 | 32.42 | 32.10 | 31.98 | 32.10 | 30.89 | 30.07 | 30.76 | 30.93 | 31.06 | 31.07 | 31.11 | 31.14 | 31.08 | 31.02 | 30.83 | 30.79 | 30.74 |
| JG | 32.19 | 31.91 | 32.52 | 32.74 | 32.98 | 32.76 | 32.40 | 32.10 | 32.32 | 32.09 | 32.63 | 32.92 | 32.61 | 31.94 | 31.80 | 31.73 | 31.71 | 32.01 | 32.31 | 32.65 | 32.80 |
| JH | 33.03 | 32.42 | 32.34 | 31.43 | 31.00 | 30.91 | 31.43 | 31.35 | 30.76 | 31.05 | 30.88 | 30.93 | 30.87 | 30.83 | 30.80 | 30.67 | 30.74 | 30.97 | 31.22 | 30.91 | 30.38 |
| JW | 31.89 | 32.58 | 32.87 | 32.59 | 33.00 | 32.17 | 31.72 | 31.61 | 31.52 | 31.75 | 31.73 | 31.73 | 31.82 | 31.96 | 32.04 | 31.89 | 31.79 | 31.64 | 31.53 | 31.82 | 31.93 |
| KW | 31.49 | 31.97 | 32.29 | 32.79 | 32.04 | 32.41 | 32.33 | 32.69 | 32.68 | 31.46 | 31.63 | 31.75 | 31.96 | 31.97 | 31.57 | 31.01 | 30.63 | 30.83 | 31.50 | 31.72 | 31.92 |
| MT | 32.67 | 33.27 | 32.56 | 32.37 | 32.22 | 32.63 | 32.54 | 32.03 | 32.13 | 31.91 | 31.24 | 31.04 | 31.14 | 31.63 | 31.66 | 31.49 | 31.42 | 31.28 | 31.27 | 31.70 | 32.09 |
| NW | 31.84 | 32.13 | 32.53 | 31.80 | 32.03 | 31.54 | 31.03 | 31.03 | 30.62 | 30.46 | 29.91 | 29.86 | 30.04 | 30.22 | 30.15 | 30.01 | 29.89 | 29.85 | 29.77 | 29.71 | 29.77 |
| SD | 32.39 | 31.73 | 32.16 | 32.71 | 32.57 | 31.72 | 31.76 | 30.90 | 31.49 | 32.21 | 31.07 | 31.58 | 31.67 | 31.60 | 31.55 | 31.61 | 31.85 | 32.18 | 31.77 | 31.37 | 31.28 |
| SL | 32.03 | 32.09 | 32.29 | 32.58 | 32.34 | 31.86 | 31.41 | 31.29 | 31.92 | 31.20 | 30.95 | 30.71 | 30.64 | 30.77 | 30.69 | 30.50 | 30.36 | 30.45 | 30.46 | 30.50 | 30.45 |

SKIN TEMPERATURE (ºC) - POMS; DAY - 1

| TIME | 0 | 5 | 10 | 15 | 20 | 25 | 30 | 35 | 40 | 45 | 50 | 51 | 52 | 53 | 54 | 55 | 56 | 57 | 58 | 59 | 60 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| AW | 31.22 | 31.13 | 31.48 | 30.99 | 31.41 | 30.57 | 30.05 | 29.95 | 29.87 | 29.57 | 29.37 | 29.47 | 29.73 | 29.62 | 29.47 | 29.41 | 29.58 | 29.81 | 29.76 | 29.66 | 29.65 |
| BA | 31.88 | 31.88 | 32.09 | 32.41 | 31.94 | 31.23 | 30.92 | 30.98 | 30.91 | 30.59 | 31.25 | 30.90 | 30.70 | 30.51 | 30.74 | 30.98 | 30.77 | 30.62 | 30.45 | 30.35 | 30.68 |
| BM | 32.23 | 32.47 | 32.51 | 32.14 | 31.94 | 31.97 | 31.67 | 31.00 | 31.04 | 30.76 | 30.45 | 30.26 | 30.06 | 29.88 | 29.80 | 30.03 | 30.20 | 30.12 | 29.97 | 29.86 | 29.85 |
| DW | 33.55 | 32.50 | 31.82 | 32.04 | 32.55 | 31.55 | 31.62 | 31.67 | 31.52 | 31.03 | 31.37 | 31.42 | 31.43 | 31.48 | 31.61 | 31.51 | 31.08 | 30.72 | 30.49 | 30.67 | 30.92 |
| JG | 32.28 | 32.98 | 32.87 | 31.86 | 32.09 | 32.80 | 32.28 | 32.02 | 31.73 | 33.23 | 32.48 | 32.74 | 32.35 | 32.10 | 31.89 | 32.01 | 32.47 | 32.81 | 32.89 | 32.81 | 32.69 |
| JH | 33.12 | 32.98 | 32.81 | 32.38 | 31.86 | 31.40 | 31.82 | 31.10 | 31.15 | 30.70 | 30.88 | 30.62 | 30.53 | 30.41 | 30.82 | 31.14 | 30.63 | 30.08 | 30.12 | 30.67 | 31.04 |
| JW | 32.50 | 32.78 | 32.77 | 32.37 | 32.62 | 31.56 | 32.21 | 31.80 | 31.21 | 32.17 | 31.59 | 31.63 | 31.93 | 31.92 | 31.81 | 31.70 | 31.64 | 31.57 | 31.66 | 31.86 | 31.72 |
| KW | 32.49 | 31.63 | 31.46 | 31.60 | 31.44 | 31.24 | 30.98 | 30.59 | 31.36 | 31.23 | 31.42 | 30.42 | 30.43 | 30.34 | 30.34 | 30.40 | 30.30 | 30.20 | 30.13 | 29.99 | 29.92 |
| MT | 33.82 | 32.92 | 31.95 | 32.04 | 32.25 | 32.66 | 32.80 | 32.15 | 32.92 | 33.21 | 33.31 | 33.35 | 33.28 | 33.24 | 33.17 | 33.08 | 32.45 | 32.02 | 32.03 | 31.22 | 31.13 |
| NW | 32.95 | 32.99 | 32.69 | 32.13 | 31.86 | 31.76 | 30.73 | 30.57 | 31.00 | 30.95 | 30.11 | 30.01 | 29.92 | 29.86 | 29.89 | 29.95 | 29.92 | 29.87 | 29.70 | 28.56 | 27.83 |
| SD | 32.24 | 31.77 | 31.70 | 32.13 | 32.32 | 31.30 | 31.29 | 31.45 | 31.58 | 31.26 | 31.04 | 30.99 | 30.96 | 30.95 | 30.96 | 31.07 | 31.01 | 30.91 | 30.75 | 30.59 | 30.50 |
| SL | 32.41 | 32.36 | 32.32 | 32.26 | 32.35 | 31.81 | 32.17 | 31.77 | 31.61 | 31.63 | 31.73 | 31.60 | 31.52 | 31.40 | 31.24 | 31.11 | 31.18 | 31.30 | 31.21 | 31.15 | 31.08 |

BODY TEMPERATURE (ºC) - PLACEBO; DAY - 1

| TIME | 0 | 5 | 10 | 15 | 20 | 25 | 30 | 35 | 40 | 45 | 50 | 51 | 52 | 53 | 54 | 55 | 56 | 57 | 58 | 59 | 60 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| AW | 36.42 | 36.47 | 36.54 | 36.67 | 36.74 | 36.82 | 36.90 | 36.92 | 36.98 | 37.13 | 37.15 | 37.14 | 37.16 | 37.19 | 37.21 | 37.22 | 37.23 | 37.26 | 37.31 | 37.32 | 37.33 |
| BA | 36.63 | 37.11 | 37.23 | 37.31 | 37.44 | 37.51 | 37.54 | 37.44 | 37.57 | 37.54 | 37.62 | 37.65 | 37.68 | 37.70 | 37.71 | 37.72 | 37.73 | 37.74 | 37.76 | 37.77 | 37.78 |
| BM | 36.27 | 36.31 | 36.49 | 36.77 | 36.97 | 37.19 | 37.30 | 37.44 | 37.53 | 37.40 | 37.41 | 37.41 | 37.47 | 37.51 | 37.55 | 37.62 | 37.67 | 37.72 | 37.80 | 37.85 | 37.82 |
| DW | 36.45 | 36.45 | 36.60 | 36.93 | 37.12 | 37.27 | 37.35 | 37.44 | 37.34 | 37.26 | 37.31 | 37.34 | 37.36 | 37.39 | 37.43 | 37.48 | 37.51 | 37.55 | 37.55 | 37.58 | 37.61 |
| JG | 36.62 | 36.69 | 36.94 | 37.16 | 37.41 | 37.60 | 37.72 | 37.80 | 37.91 | 37.93 | 38.05 | 38.10 | 38.08 | 38.03 | 38.04 | 38.08 | 38.13 | 38.23 | 38.33 | 38.43 | 38.52 |
| JH | 36.70 | 36.67 | 36.79 | 36.86 | 37.04 | 37.24 | 37.50 | 37.61 | 37.64 | 37.75 | 37.78 | 37.80 | 37.81 | 37.84 | 37.88 | 37.93 | 38.00 | 38.11 | 38.22 | 38.26 | 38.26 |
| JW | 36.87 | 36.97 | 37.05 | 37.07 | 37.21 | 37.21 | 37.25 | 37.27 | 37.28 | 37.36 | 37.32 | 37.33 | 37.34 | 37.38 | 37.41 | 37.44 | 37.47 | 37.51 | 37.55 | 37.65 | 37.73 |
| KW | 36.39 | 36.47 | 36.60 | 36.78 | 36.84 | 37.08 | 37.22 | 37.41 | 37.54 | 37.48 | 37.57 | 37.60 | 37.65 | 37.69 | 37.68 | 37.66 | 37.67 | 37.76 | 37.90 | 38.00 | 38.10 |
| MT | 37.14 | 37.33 | 37.27 | 37.35 | 37.49 | 37.69 | 37.78 | 37.79 | 37.92 | 37.93 | 37.87 | 37.85 | 37.88 | 37.97 | 38.01 | 38.02 | 38.05 | 38.06 | 38.08 | 38.16 | 38.24 |
| NW | 36.62 | 36.71 | 36.80 | 36.78 | 36.94 | 37.07 | 37.22 | 37.39 | 37.42 | 37.44 | 37.42 | 37.42 | 37.45 | 37.50 | 37.52 | 37.53 | 37.56 | 37.59 | 37.61 | 37.64 | 37.69 |
| SD | 36.39 | 36.31 | 36.50 | 36.69 | 36.83 | 36.87 | 36.97 | 36.92 | 37.05 | 37.22 | 37.11 | 37.19 | 37.23 | 37.26 | 37.30 | 37.35 | 37.42 | 37.50 | 37.47 | 37.45 | 37.46 |
| SL | 36.82 | 36.87 | 36.99 | 37.13 | 37.21 | 37.33 | 37.34 | 37.39 | 37.54 | 37.51 | 37.57 | 37.59 | 37.64 | 37.73 | 37.79 | 37.84 | 37.90 | 37.91 | 37.95 | 37.99 | 38.02 |

BODY TEMPERATURE (ºC) - POMS; DAY - 1

| TIME | 0 | 5 | 10 | 15 | 20 | 25 | 30 | 35 | 40 | 45 | 50 | 51 | 52 | 53 | 54 | 55 | 56 | 57 | 58 | 59 | 60 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| AW | 36.45 | 36.45 | 36.57 | 36.61 | 36.82 | 36.86 | 36.90 | 36.99 | 37.07 | 37.12 | 37.19 | 37.21 | 37.27 | 37.28 | 37.28 | 37.29 | 37.34 | 37.39 | 37.40 | 37.41 | 37.43 |
| BA | 36.79 | 36.78 | 36.90 | 37.10 | 37.20 | 37.25 | 37.36 | 37.46 | 37.49 | 37.46 | 37.55 | 37.50 | 37.48 | 37.47 | 37.51 | 37.53 | 37.48 | 37.44 | 37.41 | 37.40 | 37.44 |
| BM | 36.52 | 36.63 | 36.86 | 37.05 | 37.26 | 37.48 | 37.64 | 37.71 | 37.81 | 37.91 | 37.94 | 37.94 | 37.97 | 37.98 | 38.01 | 38.08 | 38.13 | 38.15 | 38.16 | 38.16 | 38.18 |
| DW | 36.53 | 36.46 | 36.55 | 36.83 | 37.09 | 37.09 | 37.19 | 37.26 | 37.25 | 37.26 | 37.36 | 37.38 | 37.38 | 37.41 | 37.45 | 37.45 | 37.44 | 37.46 | 37.50 | 37.60 | 37.71 |
| JG | 36.46 | 36.63 | 36.76 | 36.79 | 37.05 | 37.38 | 37.47 | 37.55 | 37.58 | 37.82 | 37.79 | 37.83 | 37.80 | 37.80 | 37.82 | 37.89 | 38.00 | 38.10 | 38.15 | 38.19 | 38.22 |
| JH | 36.56 | 36.56 | 36.67 | 36.77 | 36.87 | 37.03 | 37.30 | 37.35 | 37.46 | 37.46 | 37.56 | 37.55 | 37.55 | 37.58 | 37.69 | 37.79 | 37.79 | 37.80 | 37.87 | 38.02 | 38.14 |
| JW | 36.84 | 36.96 | 37.07 | 37.07 | 37.20 | 37.07 | 37.28 | 37.32 | 37.34 | 37.51 | 37.49 | 37.50 | 37.58 | 37.63 | 37.66 | 37.71 | 37.75 | 37.80 | 37.87 | 37.97 | 38.02 |
| KW | 36.52 | 36.46 | 36.50 | 36.59 | 36.65 | 36.77 | 36.87 | 37.00 | 37.20 | 37.31 | 37.39 | 37.26 | 37.30 | 37.32 | 37.35 | 37.39 | 37.42 | 37.44 | 37.45 | 37.46 | 37.50 |
| MT | 37.10 | 37.04 | 37.04 | 37.22 | 37.41 | 37.60 | 37.71 | 37.71 | 37.87 | 37.95 | 38.10 | 38.14 | 38.15 | 38.17 | 38.18 | 38.20 | 38.14 | 38.06 | 37.94 | 37.82 | 37.85 |
| NW | 36.95 | 36.92 | 36.92 | 36.96 | 37.08 | 37.28 | 37.34 | 37.39 | 37.55 | 37.74 | 37.71 | 37.74 | 37.77 | 37.78 | 37.80 | 37.82 | 37.83 | 37.84 | 37.81 | 37.56 | 37.42 |
| SD | 36.45 | 36.40 | 36.47 | 36.63 | 36.79 | 36.81 | 36.91 | 37.03 | 37.15 | 37.17 | 37.23 | 37.24 | 37.26 | 37.29 | 37.34 | 37.40 | 37.45 | 37.50 | 37.53 | 37.57 | 37.62 |
| SL | 36.67 | 36.70 | 36.82 | 36.94 | 37.10 | 37.19 | 37.42 | 37.49 | 37.59 | 37.69 | 37.74 | 37.74 | 37.74 | 37.74 | 37.75 | 37.77 | 37.83 | 37.90 | 37.94 | 37.98 | 38.03 |

BLOOD LACTATE (mmol/l) - PLACEBO; DAY - 1

| | PLACEBO | | | POMS | | |
|---|---|---|---|---|---|---|
| TIME | 5 | 30 | 60 | 5 | 30 | 60 |
| AW | 1.9 | 1.9 | 10.0 | 2.1 | 4.2 | 4.6 |
| BA | 0.8 | 1.4 | 4.3 | 0.8 | 1.6 | 2.7 |
| BM | 1.0 | 3.3 | 5.6 | 0.9 | 3.4 | 5.2 |
| DW | 1.3 | 2.1 | 5.9 | 2.1 | 2.0 | 9.7 |
| JG | 1.3 | 4.0 | 8.2 | 1.2 | 2.0 | 6.3 |
| JH | 1.0 | 2.3 | 11.6 | 1.1 | 2.8 | 11.1 |
| JW | 1.0 | 1.9 | 10.6 | 1.6 | 2.4 | 14.1 |
| KW | 1.3 | 2.6 | 9.2 | 1.6 | 1.8 | 8.2 |
| MT | 1.8 | 2.1 | 8.3 | 1.2 | 2.0 | 6.9 |
| NW | 1.4 | 3.9 | 7.3 | 1.3 | 3.4 | 8.0 |
| SD | 1.4 | 2.2 | 6.0 | 1.7 | 3.1 | 7.4 |
| SL | 1.6 | 3.7 | 11.1 | 1.0 | 3.8 | 12.4 |

RATING OF PERCEIVED EXERTION ; DAY - 1

| | PLACEBO | | POMS | |
|---|---|---|---|---|
| TIME | 30 | 45 | 30 | 45 |
| AW | 12.5 | 12.5 | 12.5 | 16.0 |
| BA | 13.0 | 13.0 | 14.0 | 16.0 |
| BM | 12.0 | 14.0 | 12.5 | 12.5 |
| DW | 14.0 | 15.0 | 14.0 | 14.0 |
| JG | 13.0 | 13.0 | 14.0 | 14.0 |
| JH | 12.0 | 12.0 | 12.0 | 13.5 |
| JW | 12.0 | 12.0 | 12.0 | 12.0 |
| KW | 14.0 | 14.0 | 13.5 | 15.0 |
| MT | 14.5 | 13.5 | 13.5 | 15.5 |
| NW | 13.0 | 14.0 | 15.0 | 14.0 |
| SD | 16.0 | 16.5 | 14.0 | 14.0 |
| SL | 13.0 | 13.0 | 13.0 | 13.0 |

AVERAGE POWER DURING TIME TRIAL (watts); DAY - 1

| Subject | PLACEBO | POMS |
|---|---|---|
| AW | 293.0 | 238.5 |
| BA | 306.5 | 261.5 |
| BM | 265.0 | 238.0 |
| DW | 270.3 | 277.5 |
| JG | 277.5 | 265.0 |
| JH | 292.8 | 295.5 |
| JW | 311.0 | 330.5 |
| KW | 379.5 | 363.8 |
| MT | 260.0 | 246.3 |
| NW | 296.0 | 261.5 |
| SD | 262.0 | 294.0 |
| SL | 287.0 | 279.0 |

OXYGEN SATURATION (%) - PLACEBO; DAY - 1

| | 5 | 10 | 15 | 20 | 25 | 30 | 35 | 40 | 45 | 50 | 51 | 52 | 53 | 54 | 55 | 56 | 57 | 58 | 59 | 60 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| JG | 57.4 | 57.0 | 54.0 | 47.8 | 46.0 | 46.6 | 46.8 | 47.5 | 50.5 | 52.4 | 50.5 | 49.5 | 48.5 | 48.1 | 47.8 | 47.8 | 48.4 | 47.6 | 47.0 | 47.6 |
| JH | 56.6 | 54.9 | 53.5 | 52.4 | 51.1 | 52.8 | 49.5 | 48.9 | 49.3 | 51.2 | 49.7 | 48.3 | 46.4 | 45.7 | 45.8 | 44.8 | 44.7 | 44.4 | 44.4 | 44.9 |
| KW | 64.7 | 63.7 | 60.6 | 57.1 | 64.0 | 61.8 | 62.1 | 63.0 | 61.7 | 60.0 | 59.4 | 58.8 | 58.4 | 58.0 | 57.8 | 57.7 | 57.4 | 57.4 | 57.9 | 57.7 |
| MT | 60.3 | 57.7 | 50.7 | 53.1 | 52.6 | 51.5 | 57.4 | 55.0 | 53.5 | 55.0 | 53.7 | 51.6 | 52.0 | 50.4 | 51.1 | 50.9 | 52.1 | 52.5 | 52.3 | 52.8 |
| SD | 65.6 | 64.5 | 61.4 | 59.1 | 60.4 | 59.6 | 60.7 | 58.2 | 57.2 | 55.7 | 56.1 | 54.9 | 55.7 | 56.8 | 56.4 | 56.7 | 56.8 | 56.1 | 56.5 | 57.1 |

OXYGEN SATURATION (%) - POMS; DAY - 1

| | 5 | 10 | 15 | 20 | 25 | 30 | 35 | 40 | 45 | 50 | 51 | 52 | 53 | 54 | 55 | 56 | 57 | 58 | 59 | 60 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| JG | 63.0 | 60.3 | 57.1 | 54.9 | 54.8 | 54.1 | 53.4 | 53.6 | 54.0 | 52.8 | 52.4 | 50.9 | 49.8 | 48.3 | 48.8 | 48.8 | 49.2 | 49.7 | 48.9 | 49.7 |
| JH | 60.2 | 56.2 | 56.1 | 54.5 | 52.6 | 51.0 | 50.5 | 50.6 | 53.6 | 52.5 | 53.2 | 53.5 | 54.4 | 53.7 | 50.8 | 51.4 | 50.2 | 50.3 | 51.0 | 49.5 |
| KW | 56.2 | 54.3 | 50.6 | 51.4 | 50.7 | 48.5 | 48.0 | 49.2 | 50.8 | 50.7 | 50.8 | 49.3 | 50.1 | 49.9 | 50.5 | 50.2 | 50.9 | 50.5 | 50.9 | 50.7 |
| MT | 58.9 | 58.7 | 55.8 | 57.6 | 57.7 | 57.2 | 61.5 | 58.7 | 55.4 | 56.9 | 57.8 | 55.8 | 57.2 | 55.5 | 56.1 | 53.6 | 54.7 | 53.9 | 56.0 | 56.5 |
| SD | 70.4 | 74.4 | 71.2 | 66.7 | 64.6 | 63.5 | 63.8 | 63.0 | 62.4 | 62.6 | 62.2 | 61.6 | 60.6 | 60.2 | 59.0 | 58.6 | 57.9 | 56.7 | 55.6 | 54.5 |

TOTAL HEMOGLOBIN CONTENT (µM) - PLACEBO; DAY - 1

| | 5 | 10 | 15 | 20 | 25 | 30 | 35 | 40 | 45 | 50 | 51 | 52 | 53 | 54 | 55 | 56 | 57 | 58 | 59 | 60 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| JG | 60.2 | 62.8 | 62.2 | 60.3 | 60.0 | 60.0 | 60.6 | 61.2 | 62.8 | 64.4 | 64.5 | 63.9 | 63.6 | 63.2 | 63.2 | 62.8 | 62.9 | 62.8 | 62.9 | 63.2 |
| JH | 63.1 | 65.9 | 66.3 | 67.3 | 68.6 | 68.9 | 68.2 | 68.8 | 68.2 | 70.2 | 70.5 | 70.8 | 69.5 | 69.3 | 70.2 | 69.5 | 69.4 | 69.8 | 69.5 | 70.2 |
| KW | 59.4 | 61.8 | 62.7 | 63.5 | 73.2 | 72.7 | 74.3 | 75.8 | 73.6 | 71.8 | 72.1 | 71.7 | 70.7 | 70.1 | 70.5 | 70.5 | 70.0 | 69.6 | 70.0 | 70.3 |
| MT | 57.2 | 55.9 | 52.8 | 53.6 | 53.1 | 53.6 | 53.4 | 51.4 | 52.9 | 53.2 | 54.2 | 54.8 | 54.0 | 53.1 | 52.5 | 53.0 | 53.2 | 54.2 | 52.5 | 53.6 |
| SD | 70.6 | 74.4 | 74.8 | 76.2 | 75.7 | 77.8 | 78.3 | 77.0 | 77.1 | 74.5 | 75.3 | 74.9 | 75.2 | 76.2 | 76.6 | 76.4 | 77.6 | 77.8 | 77.7 | 78.0 |

TOTAL HEMOGLOBIN CONTENT (µM) - POMS; DAY - 1

| | 5 | 10 | 15 | 20 | 25 | 30 | 35 | 40 | 45 | 50 | 51 | 52 | 53 | 54 | 55 | 56 | 57 | 58 | 59 | 60 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| JG | 66.7 | 70.8 | 69.4 | 68.7 | 70.5 | 70.5 | 70.8 | 70.9 | 71.7 | 69.9 | 71.2 | 69.8 | 68.6 | 68.7 | 68.3 | 69.4 | 69.8 | 70.1 | 69.2 | 69.9 |
| JH | 69.2 | 69.8 | 72.1 | 72.7 | 73.5 | 75.3 | 76.3 | 76.8 | 76.1 | 75.1 | 76.4 | 76.3 | 77.1 | 76.4 | 75.0 | 75.9 | 75.8 | 76.1 | 77.0 | 76.0 |
| KW | 62.0 | 65.2 | 65.7 | 68.3 | 65.1 | 63.4 | 64.7 | 65.9 | 65.1 | 64.5 | 65.5 | 65.8 | 67.0 | 66.6 | 67.3 | 67.2 | 67.5 | 66.9 | 67.7 | 69.2 |
| MT | 56.7 | 57.4 | 58.2 | 58.4 | 56.5 | 59.3 | 57.4 | 56.8 | 59.1 | 59.6 | 56.4 | 56.9 | 55.8 | 56.5 | 56.7 | 58.9 | 57.5 | 59.4 | 59.5 | 60.6 |
| SD | 63.9 | 72.8 | 74.0 | 70.6 | 67.9 | 67.0 | 67.7 | 66.8 | 66.6 | 66.5 | 66.3 | 65.9 | 65.7 | 66.0 | 64.8 | 64.8 | 64.2 | 64.7 | 63.5 | 62.5 |

OXYGENATED HEMOGLOBIN (µM) - PLACEBO; DAY - 1

| | 5 | 10 | 15 | 20 | 25 | 30 | 35 | 40 | 45 | 50 | 51 | 52 | 53 | 54 | 55 | 56 | 57 | 58 | 59 | 60 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| JG | 34.5 | 35.8 | 33.6 | 28.9 | 27.6 | 28.0 | 28.3 | 29.1 | 31.7 | 33.7 | 32.6 | 31.7 | 30.8 | 30.4 | 30.2 | 30.0 | 30.5 | 29.9 | 29.6 | 30.0 |
| JH | 35.7 | 36.2 | 35.5 | 35.2 | 35.1 | 36.3 | 33.8 | 33.7 | 33.6 | 35.9 | 35.1 | 34.2 | 32.3 | 31.7 | 32.2 | 31.1 | 31.1 | 31.0 | 30.9 | 31.5 |
| KW | 38.4 | 39.4 | 38.0 | 36.3 | 46.9 | 44.9 | 46.2 | 47.7 | 45.4 | 43.1 | 42.8 | 42.1 | 41.3 | 40.6 | 40.7 | 40.7 | 40.2 | 40.0 | 40.5 | 40.6 |
| MT | 34.5 | 32.3 | 26.8 | 28.5 | 28.0 | 27.6 | 30.7 | 28.3 | 28.3 | 29.2 | 29.1 | 28.3 | 28.1 | 26.7 | 26.8 | 27.0 | 27.7 | 28.4 | 27.5 | 28.3 |
| SD | 46.4 | 48.0 | 45.9 | 45.0 | 45.7 | 46.4 | 47.5 | 44.8 | 44.1 | 41.5 | 42.2 | 41.1 | 41.9 | 43.3 | 43.2 | 43.3 | 44.1 | 43.7 | 43.9 | 44.6 |

OXYGENATED HEMOGLOBIN (µM) - POMS; DAY - 1

| | 5 | 10 | 15 | 20 | 25 | 30 | 35 | 40 | 45 | 50 | 51 | 52 | 53 | 54 | 55 | 56 | 57 | 58 | 59 | 60 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| JG | 42.0 | 42.7 | 39.6 | 37.7 | 38.7 | 38.2 | 37.8 | 38.0 | 38.7 | 36.9 | 37.3 | 35.5 | 34.2 | 33.2 | 33.3 | 33.8 | 34.4 | 34.8 | 33.8 | 34.8 |
| JH | 41.6 | 39.2 | 40.5 | 39.6 | 38.7 | 38.4 | 38.5 | 38.9 | 40.7 | 39.4 | 40.6 | 40.8 | 41.9 | 41.1 | 38.1 | 39.0 | 38.0 | 38.3 | 39.2 | 37.6 |
| KW | 34.9 | 35.4 | 33.2 | 35.1 | 33.1 | 30.7 | 31.1 | 32.4 | 33.0 | 32.7 | 33.3 | 32.4 | 33.5 | 33.2 | 34.0 | 33.7 | 34.3 | 33.8 | 34.4 | 35.1 |
| MT | 33.4 | 33.7 | 32.5 | 33.6 | 32.6 | 34.0 | 35.2 | 33.4 | 32.7 | 33.9 | 32.6 | 31.7 | 31.9 | 31.3 | 31.8 | 31.6 | 31.4 | 32.0 | 33.3 | 34.2 |
| SD | 45.0 | 54.2 | 52.7 | 47.1 | 43.9 | 42.5 | 43.2 | 42.0 | 41.6 | 41.6 | 41.3 | 40.6 | 39.8 | 39.7 | 38.2 | 38.0 | 37.1 | 36.7 | 35.3 | 34.0 |

DEOXYGENATED HEMOGLOBIN (µM) - PLACEBO; DAY - 1

| | 5 | 10 | 15 | 20 | 25 | 30 | 35 | 40 | 45 | 50 | 51 | 52 | 53 | 54 | 55 | 56 | 57 | 58 | 59 | 60 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| JG | 25.7 | 27.0 | 28.6 | 31.5 | 32.5 | 32.0 | 32.3 | 32.1 | 31.1 | 30.6 | 31.9 | 32.3 | 32.8 | 32.8 | 33.0 | 32.8 | 32.5 | 32.9 | 33.3 | 33.1 |
| JH | 27.4 | 29.7 | 30.8 | 32.1 | 33.5 | 32.5 | 34.4 | 35.1 | 34.6 | 34.2 | 35.4 | 36.6 | 37.3 | 37.6 | 38.0 | 38.3 | 38.4 | 38.8 | 38.6 | 38.7 |
| KW | 21.0 | 22.4 | 24.7 | 27.3 | 26.3 | 27.7 | 28.2 | 28.1 | 28.2 | 28.7 | 29.3 | 29.5 | 29.4 | 29.4 | 29.8 | 29.8 | 29.8 | 29.6 | 29.5 | 29.7 |
| MT | 22.7 | 23.6 | 26.0 | 25.1 | 25.1 | 26.0 | 22.7 | 23.1 | 24.6 | 23.9 | 25.1 | 26.5 | 25.9 | 26.4 | 25.7 | 26.0 | 25.5 | 25.8 | 25.0 | 25.3 |
| SD | 24.3 | 26.4 | 28.8 | 31.1 | 30.0 | 31.4 | 30.8 | 32.1 | 33.0 | 33.0 | 33.1 | 33.8 | 33.4 | 32.9 | 33.4 | 33.1 | 33.5 | 34.0 | 33.7 | 33.5 |

DEOXYGENATED HEMOGLOBIN (µM) - POMS; DAY - 1

| | 5 | 10 | 15 | 20 | 25 | 30 | 35 | 40 | 45 | 50 | 51 | 52 | 53 | 54 | 55 | 56 | 57 | 58 | 59 | 60 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| JG | 24.7 | 28.1 | 29.7 | 31.0 | 31.8 | 32.3 | 33.0 | 32.9 | 33.0 | 33.0 | 33.9 | 34.3 | 34.4 | 35.5 | 35.0 | 35.6 | 35.5 | 35.3 | 35.4 | 35.1 |
| JH | 27.5 | 30.6 | 31.7 | 33.1 | 34.9 | 36.9 | 37.7 | 37.9 | 35.3 | 35.7 | 35.7 | 35.5 | 35.2 | 35.3 | 36.9 | 36.8 | 37.7 | 37.8 | 37.7 | 38.4 |
| KW | 27.2 | 29.8 | 32.5 | 33.2 | 32.1 | 32.7 | 33.6 | 33.5 | 32.0 | 31.8 | 32.2 | 33.4 | 33.5 | 33.4 | 33.3 | 33.5 | 33.2 | 33.1 | 33.3 | 34.1 |
| MT | 23.3 | 23.7 | 25.7 | 24.8 | 23.9 | 25.4 | 22.1 | 23.5 | 26.4 | 25.7 | 23.8 | 25.2 | 23.9 | 25.2 | 24.9 | 27.3 | 26.0 | 27.4 | 26.2 | 26.4 |
| SD | 18.9 | 18.6 | 21.3 | 23.5 | 24.0 | 24.5 | 24.5 | 24.7 | 25.0 | 24.9 | 25.0 | 25.3 | 25.9 | 26.3 | 26.6 | 26.8 | 27.0 | 28.0 | 28.3 | 28.4 |

| | MAXIMAL NUEROMUSCULAR POWER; DAY - 1 | | | | | |
|---|---|---|---|---|---|---|
| | INSTANTANEOUS POWER (watts) | | MAXIMAL POWER (watts) | | REVOLUTIONS PER MINUTE | |
| Subject | PLACEBO | POMS | PLACEBO | POMS | PLACEBO | POMS |
| AW | 1797.6 | 1723.6 | 1084.7 | 1091.3 | 127.9 | 123.9 |
| BA | 1965.6 | 1885.8 | 1294.5 | 1191.6 | 127.7 | 125.9 |
| BM | 1401.6 | 1470.7 | 876.3 | 891.2 | 115.1 | 120.8 |
| DW | 1733.0 | 1671.0 | 1068.5 | 978.9 | 114.9 | 113.6 |
| JG | 1927.1 | 1904.3 | 1155.2 | 1164.8 | 124.4 | 130.3 |
| JH | 1982.9 | 2079.7 | 1223.9 | 1258.2 | 112.5 | 115.5 |
| JW | 2290.0 | 2440.1 | 1323.5 | 1401.8 | 113.6 | 119.3 |
| KW | 2768.7 | 2739.7 | 1740.1 | 1768.1 | 106.5 | 100.4 |
| MT | 1691.2 | 1857.6 | 1073.7 | 1119.7 | 134.8 | 130.6 |
| NW | 1976.7 | 2007.1 | 1225.0 | 1257.0 | 127.9 | 129.6 |
| SD | 2576.5 | 2420.0 | 1504.5 | 1370.6 | 129.0 | 122.7 |
| SL | 2216.5 | 2153.7 | 1427.2 | 1382.3 | 116.1 | 116.0 |

HEART RATE (bpm) - PLACEBO; DAY - 2

| TIME | 0 | 10 | 20 | 30 | 40 | 50 | 60 | 70 | 80 | 90 | 100 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| AW | 183.4 | 187.0 | 187.6 | 188.6 | 192.3 | 196.4 | 197.2 | 197.9 | 198.4 | 197.9 | 198.4 |
| BA | 120.9 | 124.0 | 130.5 | 135.4 | 138.6 | 139.5 | 141.4 | 143.5 | 145.5 | 147.3 | 147.6 |
| BM | 158.0 | 160.0 | 165.8 | 170.9 | 172.6 | 173.7 | 176.0 | 177.9 | 179.7 | 180.7 | 181.2 |
| DW | 154.3 | 160.3 | 167.8 | 171.6 | 175.8 | 179.0 | 179.8 | 181.1 | 182.6 | 183.0 | 184.3 |
| JG | 156.3 | 159.9 | 164.0 | 168.0 | 171.0 | 172.4 | 172.9 | 174.3 | 175.9 | 176.4 | 173.9 |
| JH | 151.8 | 161.4 | 171.5 | 177.1 | 180.2 | 182.0 | 183.9 | 185.4 | 187.0 | 187.7 | 187.7 |
| JW | 140.4 | 149.2 | 158.5 | 164.1 | 168.0 | 171.0 | 174.0 | 177.4 | 179.9 | 185.6 | 187.2 |
| KW | 156.3 | 162.8 | 171.8 | 177.1 | 180.3 | 181.5 | 182.4 | 184.0 | 185.5 | 187.0 | 188.6 |
| MT | 160.3 | 160.3 | 167.9 | 170.5 | 173.9 | 176.3 | 178.2 | 180.0 | 180.5 | 181.1 | 180.9 |
| NW | 152.2 | 157.8 | 164.1 | 166.7 | 170.1 | 170.8 | 173.3 | 175.2 | 177.3 | 178.3 | 180.4 |
| SD | 164.1 | 167.7 | 173.3 | 175.7 | 176.8 | 180.3 | 182.3 | 183.3 | 183.1 | 183.6 | 184.2 |
| SL | 156.1 | 158.9 | 165.3 | 168.4 | 171.0 | 173.1 | 174.5 | 175.8 | 177.2 | 179.0 | 180.3 |

HEART RATE (bpm) - POMS; DAY - 2

| TIME | 0 | 10 | 20 | 30 | 40 | 50 | 60 | 70 | 80 | 90 | 100 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| AW | 189.3 | 192.5 | 193.9 | 197.4 | 200.0 | 201.7 | 202.7 | 204.1 | 204.7 | 206.6 | 206.5 |
| BA | 128.2 | 127.4 | 131.9 | 137.3 | 139.9 | 143.1 | 145.9 | 147.9 | 149.4 | 150.6 | 150.3 |
| BM | 156.9 | 162.3 | 169.8 | 173.0 | 175.3 | 176.5 | 177.6 | 180.2 | 181.1 | 181.7 | 182.6 |
| DW | 147.3 | 154.4 | 162.9 | 169.2 | 171.5 | 174.1 | 175.9 | 179.0 | 179.8 | 180.8 | 182.8 |
| JG | 156.6 | 159.3 | 164.0 | 167.5 | 170.0 | 170.7 | 170.9 | 172.1 | 174.0 | 175.2 | 174.4 |
| JH | 154.1 | 161.9 | 170.1 | 174.9 | 177.1 | 179.8 | 182.7 | 184.2 | 186.1 | 186.7 | 187.5 |
| JW | 145.4 | 149.7 | 158.7 | 163.6 | 167.9 | 170.1 | 172.4 | 175.5 | 178.9 | 182.7 | 185.7 |
| KW | 151.9 | 157.4 | 163.8 | 170.2 | 173.0 | 175.2 | 176.4 | 177.7 | 176.5 | 179.4 | 182.1 |
| MT | 166.9 | 170.7 | 173.7 | 178.7 | 181.0 | 182.1 | 184.3 | 184.0 | 184.1 | 184.0 | 185.3 |
| NW | 157.1 | 161.8 | 167.9 | 170.5 | 172.4 | 174.3 | 175.9 | 178.2 | 179.7 | 181.4 | 182.4 |
| SD | 163.1 | 165.2 | 170.7 | 172.4 | 174.7 | 175.7 | 177.8 | 177.2 | 177.2 | 177.7 | 177.9 |
| SL | 154.7 | 157.9 | 163.2 | 168.0 | 170.1 | 173.1 | 174.9 | 176.2 | 177.1 | 179.2 | 180.3 |

STROKE VOLUME (ml/beat) - PLACEBO; DAY - 2

| TIME | 0 | 10 | 20 | 30 | 40 | 50 | 60 | 70 | 80 | 90 | 100 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| AW | 119.9 | 112.5 | 114.2 | 113.2 | 111.8 | 117.4 | 112.9 | 108.3 | 110.7 | 113.0 | 115.7 |
| BA | 140.0 | 137.4 | 140.3 | 140.3 | 141.6 | 143.0 | 145.3 | 142.8 | 137.7 | 134.2 | 141.2 |
| BM | 139.0 | 139.6 | 143.0 | 141.6 | 140.6 | 139.7 | 138.4 | 135.4 | 138.7 | 129.4 | 134.8 |
| DW | 117.6 | 129.6 | 128.9 | 132.6 | 135.3 | 134.3 | 131.3 | 134.2 | 127.9 | 132.0 | 129.3 |
| JG | 116.4 | 122.6 | 117.4 | 119.9 | 122.8 | 117.7 | 116.2 | 114.3 | 117.9 | 111.8 | 121.6 |
| JH | 109.8 | 114.4 | 113.4 | 112.5 | 110.9 | 115.3 | 116.8 | 107.2 | 112.6 | 114.8 | 109.3 |
| JW | 154.0 | 153.1 | 149.5 | 157.5 | 161.1 | 156.3 | 158.2 | 157.8 | 163.8 | 176.1 | 166.3 |
| KW | 131.5 | 129.5 | 129.1 | 131.3 | 132.4 | 129.9 | 130.3 | 128.3 | 126.3 | 128.8 | 131.9 |
| MT | 132.3 | 137.7 | 137.2 | 137.4 | 132.1 | 128.0 | 132.7 | 137.2 | 136.0 | 135.0 | 134.9 |
| NW | 130.5 | 137.6 | 137.5 | 133.6 | 137.6 | 136.6 | 133.8 | 135.7 | 132.8 | 135.0 | 134.5 |
| SD | 109.1 | 105.0 | 107.2 | 105.9 | 104.2 | 106.2 | 107.8 | 106.4 | 112.1 | 109.1 | 107.0 |
| SL | 127.1 | 134.8 | 135.7 | 137.7 | 134.9 | 139.4 | 138.5 | 135.7 | 138.5 | 135.8 | 139.3 |

STROKE VOLUME (ml/beat) - POMS; DAY - 2

| TIME | 0 | 10 | 20 | 30 | 40 | 50 | 60 | 70 | 80 | 90 | 100 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| AW | 107.7 | 100.1 | 98.5 | 100.2 | 99.3 | 101.1 | 104.4 | 102.3 | 103.6 | 99.1 | 98.4 |
| BA | 131.8 | 132.1 | 133.7 | 130.9 | 137.7 | 135.9 | 132.7 | 126.1 | 134.9 | 136.8 | 135.9 |
| BM | 140.3 | 142.2 | 149.3 | 144.5 | 146.1 | 148.4 | 142.5 | 141.0 | 147.6 | 143.0 | 134.4 |
| DW | 120.2 | 130.7 | 128.9 | 127.8 | 127.8 | 129.1 | 127.8 | 125.3 | 127.6 | 133.9 | 134.5 |
| JG | 131.7 | 125.1 | 120.2 | 134.6 | 132.4 | 130.1 | 125.0 | 124.8 | 132.9 | 126.1 | 124.3 |
| JH | 137.2 | 137.4 | 138.1 | 138.2 | 143.8 | 146.0 | 143.7 | 145.8 | 143.9 | 144.2 | 145.8 |
| JW | 133.2 | 142.3 | 143.5 | 141.6 | 140.5 | 144.3 | 135.7 | 146.3 | 141.5 | 150.9 | 150.4 |
| KW | 147.5 | 149.4 | 154.1 | 153.7 | 152.2 | 154.0 | 153.6 | 152.3 | 148.0 | 149.6 | 149.6 |
| MT | 123.6 | 126.2 | 122.9 | 126.4 | 119.9 | 125.8 | 128.5 | 128.7 | 122.0 | 122.9 | 119.2 |
| NW | 140.4 | 144.7 | 145.5 | 145.5 | 146.1 | 147.2 | 146.4 | 143.1 | 143.0 | 147.0 | 145.0 |
| SD | 105.6 | 109.9 | 108.0 | 105.3 | 104.1 | 104.7 | 109.6 | 107.6 | 108.8 | 106.2 | 109.5 |
| SL | 135.7 | 142.9 | 143.4 | 144.0 | 145.1 | 143.4 | 145.9 | 149.3 | 141.0 | 144.9 | 145.6 |

CARDIAC OUTPUT (l/min) - PLACEBO; DAY - 2

| TIME | 0 | 10 | 20 | 30 | 40 | 50 | 60 | 70 | 80 | 90 | 100 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| AW | 22.0 | 21.0 | 21.4 | 21.3 | 21.5 | 23.1 | 22.3 | 21.4 | 22.0 | 22.4 | 23.0 |
| BA | 16.9 | 17.0 | 18.3 | 19.0 | 19.6 | 20.0 | 20.5 | 20.5 | 20.0 | 19.8 | 20.8 |
| BM | 22.0 | 22.3 | 23.7 | 24.2 | 24.3 | 24.3 | 24.4 | 24.1 | 24.9 | 23.4 | 24.4 |
| DW | 18.1 | 20.8 | 21.6 | 22.8 | 23.8 | 24.0 | 23.6 | 24.3 | 23.3 | 24.1 | 23.8 |
| JG | 18.2 | 19.6 | 19.3 | 20.1 | 21.0 | 20.3 | 20.1 | 19.9 | 20.7 | 19.7 | 21.1 |
| JH | 16.7 | 18.5 | 19.4 | 19.9 | 20.0 | 21.0 | 21.5 | 19.9 | 21.1 | 21.5 | 20.5 |
| JW | 21.6 | 22.8 | 23.7 | 25.9 | 27.1 | 26.7 | 27.5 | 28.0 | 29.4 | 32.1 | 30.5 |
| KW | 20.6 | 21.1 | 22.2 | 23.3 | 23.9 | 23.6 | 23.8 | 23.6 | 23.4 | 24.1 | 24.9 |
| MT | 21.2 | 22.1 | 23.0 | 23.4 | 23.0 | 22.6 | 23.6 | 24.7 | 24.6 | 24.5 | 24.4 |
| NW | 19.9 | 21.7 | 22.6 | 22.3 | 23.4 | 23.3 | 23.2 | 23.8 | 23.5 | 24.1 | 24.3 |
| SD | 17.9 | 17.6 | 18.6 | 18.6 | 18.4 | 19.1 | 19.6 | 19.5 | 20.5 | 20.0 | 19.7 |
| SL | 19.8 | 21.4 | 22.4 | 23.2 | 23.1 | 24.1 | 24.2 | 23.9 | 24.6 | 24.3 | 25.1 |

CARDIAC OUTPUT (l/min) - POMS; DAY - 2

| TIME | 0 | 10 | 20 | 30 | 40 | 50 | 60 | 70 | 80 | 90 | 100 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| AW | 20.4 | 19.3 | 19.1 | 19.8 | 19.8 | 20.4 | 21.2 | 20.9 | 21.2 | 20.5 | 20.3 |
| BA | 16.9 | 16.8 | 17.6 | 18.0 | 19.3 | 19.4 | 19.4 | 18.6 | 20.2 | 20.6 | 20.4 |
| BM | 22.0 | 23.1 | 25.3 | 25.0 | 25.6 | 26.2 | 25.3 | 25.4 | 26.7 | 26.0 | 24.5 |
| DW | 17.7 | 20.2 | 21.0 | 21.6 | 21.9 | 22.5 | 22.5 | 22.4 | 22.9 | 24.2 | 24.6 |
| JG | 20.6 | 19.9 | 19.7 | 22.5 | 22.5 | 22.2 | 21.4 | 21.5 | 23.1 | 22.1 | 21.7 |
| JH | 21.1 | 22.2 | 23.5 | 24.2 | 25.5 | 26.3 | 26.2 | 26.8 | 26.8 | 26.9 | 27.3 |
| JW | 19.4 | 21.3 | 22.8 | 23.2 | 23.6 | 24.5 | 23.4 | 25.7 | 25.3 | 27.6 | 27.9 |
| KW | 22.4 | 23.5 | 25.2 | 26.2 | 26.3 | 27.0 | 27.1 | 27.1 | 26.1 | 26.8 | 27.2 |
| MT | 20.6 | 21.5 | 21.3 | 22.6 | 21.7 | 22.9 | 23.7 | 23.7 | 22.5 | 22.6 | 22.1 |
| NW | 22.1 | 23.4 | 24.4 | 24.8 | 25.2 | 25.7 | 25.7 | 25.5 | 25.7 | 26.7 | 26.5 |
| SD | 17.2 | 18.1 | 18.4 | 18.2 | 18.2 | 18.4 | 19.5 | 19.1 | 19.3 | 18.9 | 19.5 |
| SL | 21.0 | 22.6 | 23.4 | 24.2 | 24.7 | 24.8 | 25.5 | 26.3 | 25.0 | 26.0 | 26.3 |

VENTILATION (l/min) - PLACEBO; DAY - 2

| TIME | 0 | 10 | 20 | 30 | 40 | 50 | 60 | 70 | 80 | 90 | 100 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| AW | 85.3 | 85.2 | 80.3 | 100.4 | 98.8 | 106.8 | 109.5 | 121.4 | 119.2 | 117.9 | 116.8 |
| BA | 62.1 | 64.2 | 70.6 | 83.0 | 84.2 | 97.3 | 99.8 | 107.6 | 116.3 | 134.7 | 122.9 |
| BM | 72.0 | 89.2 | 107.0 | 124.1 | 124.3 | 133.7 | 138.7 | 146.6 | 140.1 | 141.1 | 124.2 |
| DW | 68.8 | 75.4 | 94.3 | 98.9 | 106.9 | 113.9 | 120.7 | 121.1 | 128.3 | 127.3 | 128.1 |
| JG | 66.2 | 85.1 | 106.1 | 115.7 | 117.8 | 120.3 | 121.0 | 119.2 | 125.3 | 109.0 | 110.7 |
| JH | 64.5 | 84.8 | 100.4 | 107.9 | 110.9 | 115.7 | 113.0 | 120.0 | 118.4 | 107.0 | 112.7 |
| JW | 64.4 | 77.2 | 93.3 | 103.5 | 113.7 | 119.8 | 117.1 | 124.1 | 127.6 | 124.6 | 126.2 |
| KW | 87.0 | 105.2 | 121.1 | 127.0 | 128.8 | 136.3 | 132.1 | 133.3 | 140.4 | 144.4 | 148.9 |
| MT | 67.1 | 71.7 | 72.2 | 86.9 | 98.4 | 98.4 | 98.6 | 107.2 | 108.3 | 109.7 | 105.4 |
| NW | 68.2 | 84.5 | 95.8 | 106.8 | 107.1 | 114.5 | 115.2 | 115.2 | 121.9 | 120.8 | 105.4 |
| SD | 76.3 | 85.6 | 89.6 | 105.1 | 104.3 | 104.6 | 110.9 | 111.8 | 110.9 | 125.9 | 118.8 |

VENTILATION (l/min) - POMS; DAY - 2

| TIME | 0 | 10 | 20 | 30 | 40 | 50 | 60 | 70 | 80 | 90 | 100 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| AW | 73.4 | 92.4 | 103.4 | 100.9 | 114.3 | 121.7 | 121.3 | 124.0 | 126.1 | 125.3 | 125.1 |
| BA | 67.7 | 75.1 | 86.3 | 87.7 | 100.5 | 113.5 | 125.6 | 129.9 | 132.7 | 146.1 | 119.1 |
| BM | 71.8 | 89.7 | 106.9 | 117.1 | 120.9 | 121.6 | 130.2 | 133.4 | 136.7 | 136.8 | 128.4 |
| DW | 66.2 | 78.5 | 101.1 | 117.9 | 114.1 | 124.8 | 116.2 | 119.3 | 121.4 | 127.9 | 124.4 |
| JG | 78.5 | 84.5 | 86.5 | 104.5 | 108.4 | 105.4 | 112.4 | 116.8 | 120.8 | 128.5 | 127.3 |
| JH | 71.9 | 95.6 | 109.1 | 109.0 | 119.4 | 122.6 | 125.3 | 125.6 | 121.5 | 120.5 | 121.0 |
| JW | 68.5 | 85.6 | 93.9 | 108.8 | 116.8 | 121.3 | 125.6 | 126.3 | 123.4 | 118.8 | 115.0 |
| KW | 120.6 | 119.5 | 128.2 | 135.2 | 141.5 | 142.9 | 145.1 | 137.7 | 146.4 | 149.1 | 145.5 |
| MT | 68.5 | 73.2 | 83.3 | 94.2 | 95.0 | 104.0 | 102.0 | 94.9 | 97.1 | 104.1 | 103.4 |
| NW | 65.6 | 82.9 | 95.4 | 102.5 | 107.9 | 109.5 | 116.6 | 113.8 | 116.7 | 115.3 | 111.8 |
| SD | 82.6 | 84.5 | 94.1 | 100.1 | 106.5 | 115.3 | 118.6 | 117.6 | 116.7 | 119.3 | 121.8 |
| SL | 69.3 | 78.8 | 90.9 | 104.1 | 114.4 | 118.9 | 126.4 | 128.2 | 140.1 | 144.9 | 145.1 |

OXYGEN CONSUMPTIONS (l/min) - PLACEBO; DAY - 2

| TIME | 0 | 10 | 20 | 30 | 40 | 50 | 60 | 70 | 80 | 90 | 100 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| AW | 3712 | 3763 | 3593 | 4019 | 4049 | 4084 | 4163 | 4375 | 4367 | 4341 | 4330 |
| BA | 3298 | 3443 | 3683 | 3839 | 3902 | 4020 | 3850 | 3951 | 4039 | 4303 | 4134 |
| BM | 3248 | 3667 | 3871 | 4148 | 4145 | 4257 | 4328 | 4404 | 4183 | 4088 | 3663 |
| DW | 3116 | 3426 | 3802 | 3843 | 4016 | 4116 | 4157 | 4188 | 4289 | 4145 | 4138 |
| JG | 2979 | 3528 | 3939 | 4090 | 4156 | 4132 | 4122 | 4118 | 4065 | 3707 | 3646 |
| JH | 3241 | 3786 | 4023 | 4193 | 4294 | 4431 | 4405 | 4559 | 4486 | 4235 | 4360 |
| JW | 3286 | 3637 | 3867 | 4098 | 4370 | 4427 | 4335 | 4646 | 4589 | 4373 | 4493 |
| KW | 3962 | 4413 | 4833 | 4987 | 4914 | 5187 | 4911 | 4964 | 5151 | 5320 | 5285 |
| MT | 3237 | 3308 | 3111 | 3536 | 3891 | 3878 | 3828 | 4301 | 4216 | 4401 | 4145 |
| NW | 3545 | 3971 | 4120 | 4615 | 4663 | 4715 | 4403 | 4356 | 4787 | 4596 | 3862 |
| SD | 3587 | 3881 | 3808 | 4334 | 4169 | 4101 | 4228 | 4303 | 4220 | 4749 | 4497 |

OXYGEN CONSUMPTION (l/min) - POMS; DAY - 2

| TIME | 0 | 10 | 20 | 30 | 40 | 50 | 60 | 70 | 80 | 90 | 100 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| AW | 3147 | 3830 | 3949 | 3910 | 4138 | 4196 | 4217 | 4242 | 4278 | 4281 | 4263 |
| BA | 3090 | 3544 | 3805 | 3782 | 3968 | 4089 | 4371 | 4319 | 4116 | 4301 | 3896 |
| BM | 3122 | 3376 | 3571 | 3687 | 3945 | 3990 | 3903 | 4051 | 4152 | 4128 | 3896 |
| DW | 2979 | 3395 | 3898 | 4082 | 4070 | 4242 | 4028 | 4163 | 4038 | 4186 | 4143 |
| JG | 3340 | 3433 | 3270 | 3808 | 4051 | 3841 | 4021 | 3998 | 4096 | 4391 | 4317 |
| JH | 3295 | 3818 | 4135 | 4173 | 4357 | 4491 | 4512 | 4495 | 4350 | 4495 | 4422 |
| JW | 3555 | 3940 | 3896 | 4520 | 4702 | 4781 | 4909 | 4842 | 4787 | 4615 | 4482 |
| KW | 4392 | 4482 | 4948 | 5100 | 5253 | 5304 | 5330 | 5128 | 5179 | 5185 | 4872 |
| MT | 3369 | 3323 | 3660 | 3732 | 3852 | 4004 | 4051 | 3659 | 3823 | 3961 | 3832 |
| NW | 3486 | 4006 | 4228 | 4367 | 4444 | 4470 | 4488 | 4441 | 4395 | 4175 | 3871 |
| SD | 3906 | 3891 | 4171 | 4316 | 4366 | 4612 | 4528 | 4564 | 4563 | 4573 | 4633 |
| SL | 3140 | 3367 | 3533 | 3708 | 3899 | 3986 | 3924 | 4084 | 4194 | 4085 | 3923 |

RESPIRATORY EXCHANGE RATION - PLACEBO; DAY - 2

| TIME | 0 | 10 | 20 | 30 | 40 | 50 | 60 | 70 | 80 | 90 | 100 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| AW | 0.95 | 0.95 | 0.98 | 1.03 | 1.03 | 1.06 | 1.05 | 1.07 | 1.05 | 1.04 | 1.03 |
| BA | 0.84 | 0.83 | 0.86 | 0.80 | 0.96 | 0.99 | 1.03 | 1.03 | 1.03 | 1.04 | 1.02 |
| BM | 0.90 | 0.96 | 1.05 | 1.10 | 1.07 | 1.06 | 1.04 | 1.04 | 1.02 | 1.02 | 1.02 |
| DW | 0.94 | 0.98 | 1.08 | 1.11 | 1.11 | 1.09 | 1.08 | 1.07 | 1.05 | 1.04 | 1.03 |
| JG | 0.91 | 0.98 | 1.09 | 1.08 | 1.07 | 1.05 | 1.03 | 1.01 | 1.01 | 1.01 | 1.02 |
| JH | 0.99 | 1.10 | 1.16 | 1.13 | 1.08 | 1.04 | 1.00 | 1.00 | 0.97 | 0.97 | 0.97 |
| JW | 0.89 | 0.99 | 1.09 | 1.10 | 1.08 | 1.07 | 1.06 | 1.03 | 1.06 | 1.06 | 1.05 |
| KW | 0.91 | 0.97 | 1.02 | 1.01 | 1.00 | 0.98 | 0.97 | 0.96 | 0.94 | 0.97 | 0.98 |
| MT | 0.97 | 0.99 | 1.05 | 1.07 | 1.08 | 1.06 | 1.07 | 1.05 | 1.04 | 1.02 | 1.02 |
| NW | 0.86 | 0.94 | 0.98 | 1.01 | 0.99 | 1.02 | 1.02 | 1.01 | 0.98 | 1.00 | 1.03 |
| SD | 0.87 | 0.93 | 0.96 | 0.94 | 0.93 | 0.92 | 0.91 | 0.90 | 0.89 | 0.89 | 0.88 |

RESPIRATORY EXCHANGE RATIO - POMS; DAY - 2

| TIME | 0 | 10 | 20 | 30 | 40 | 50 | 60 | 70 | 80 | 90 | 100 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| AW | 0.92 | 0.95 | 1.01 | 1.01 | 1.06 | 1.07 | 1.06 | 1.05 | 1.05 | 1.04 | 1.03 |
| BA | 0.96 | 0.89 | 0.94 | 1.00 | 1.01 | 1.05 | 1.06 | 1.08 | 1.07 | 1.06 | 1.06 |
| BM | 0.94 | 0.89 | 1.07 | 1.06 | 1.03 | 1.02 | 1.04 | 1.03 | 1.00 | 1.00 | 0.99 |
| DW | 0.91 | 0.95 | 1.06 | 1.11 | 1.07 | 1.06 | 1.04 | 1.01 | 1.01 | 1.01 | 1.00 |
| JG | 0.87 | 0.90 | 0.95 | 0.98 | 0.95 | 0.99 | 0.98 | 1.00 | 0.98 | 0.97 | 0.98 |
| JH | 0.98 | 1.11 | 1.12 | 1.07 | 1.06 | 1.02 | 1.00 | 0.99 | 0.96 | 0.95 | 0.95 |
| JW | 0.87 | 0.97 | 1.05 | 1.05 | 1.05 | 1.03 | 1.01 | 1.01 | 0.99 | 0.99 | 1.00 |
| KW | 0.94 | 0.95 | 0.95 | 0.97 | 0.99 | 0.98 | 0.97 | 0.96 | 0.98 | 0.97 | 1.00 |
| MT | 0.93 | 0.99 | 1.04 | 1.08 | 1.07 | 1.06 | 1.04 | 1.00 | 0.98 | 0.98 | 0.98 |
| NW | 0.87 | 0.97 | 1.03 | 1.03 | 1.01 | 0.99 | 0.99 | 0.98 | 0.98 | 0.99 | 1.03 |
| SD | 0.87 | 0.91 | 0.96 | 0.97 | 0.99 | 0.99 | 1.00 | 0.96 | 0.93 | 0.95 | 0.96 |
| SL | 0.93 | 0.98 | 1.07 | 1.11 | 1.11 | 1.08 | 1.08 | 1.03 | 1.04 | 1.04 | 1.04 |

CORE TEMPERATURE(ºC) - PLACEBO; DAY - 2

| TIME | 0 | 10 | 20 | 30 | 40 | 50 | 60 | 70 | 80 | 90 | 100 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| BA | 37.91 | 37.91 | 37.92 | 37.94 | 37.95 | 37.97 | 37.99 | 38.01 | 38.03 | 38.05 | 38.07 |
| BM | 37.60 | 37.62 | 37.65 | 37.69 | 37.74 | 37.79 | 37.84 | 37.89 | 37.94 | 38.00 | 38.05 |
| DW | 37.71 | 37.72 | 37.76 | 37.81 | 37.87 | 37.94 | 38.02 | 38.08 | 38.15 | 38.23 | 38.31 |
| JG | 37.52 | 37.54 | 37.57 | 37.60 | 37.63 | 37.67 | 37.71 | 37.74 | 37.78 | 37.83 | 37.88 |
| JH | 37.75 | 37.82 | 37.88 | 37.98 | 38.10 | 38.25 | 38.40 | 38.56 | 38.74 | 38.91 | 39.06 |
| JW | 37.65 | 37.66 | 37.69 | 37.73 | 37.79 | 37.85 | 37.92 | 37.99 | 38.07 | 38.14 | 38.22 |
| KW | 37.89 | 37.93 | 37.96 | 38.00 | 38.03 | 38.07 | 38.11 | 38.14 | 38.19 | 38.24 | 38.29 |
| MT | 37.97 | 38.00 | 38.02 | 38.04 | 38.07 | 38.10 | 38.13 | 38.16 | 38.19 | 38.22 | 38.26 |
| NW | 37.51 | 37.54 | 37.57 | 37.63 | 37.68 | 37.75 | 37.83 | 37.91 | 37.98 | 38.07 | 38.16 |
| SD | 37.37 | 37.40 | 37.46 | 37.53 | 37.60 | 37.68 | 37.77 | 37.85 | 37.94 | 38.03 | 38.12 |
| SL | 37.94 | 37.95 | 37.98 | 38.00 | 38.03 | 38.07 | 38.11 | 38.15 | 38.20 | 38.25 | 38.31 |

CORE TEMPERATURE(ºC) - POMS; DAY - 2

| TIME | 0 | 10 | 20 | 30 | 40 | 50 | 60 | 70 | 80 | 90 | 100 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| AW | 37.93 | 37.94 | 37.96 | 37.98 | 38.01 | 38.03 | 38.06 | 38.08 | 38.11 | 38.13 | 38.17 |
| BA | 38.02 | 38.03 | 38.04 | 38.06 | 38.08 | 38.11 | 38.13 | 38.16 | 38.19 | 38.21 | 38.24 |
| BM | 37.85 | 37.87 | 37.91 | 37.94 | 37.98 | 38.03 | 38.08 | 38.14 | 38.20 | 38.26 | 38.34 |
| DW | 37.39 | 37.40 | 37.44 | 37.49 | 37.55 | 37.61 | 37.68 | 37.75 | 37.83 | 37.91 | 37.98 |
| JG | 37.94 | 37.95 | 37.98 | 38.00 | 38.03 | 38.05 | 38.08 | 38.10 | 38.14 | 38.17 | 38.20 |
| JH | 37.82 | 37.91 | 38.00 | 38.13 | 38.29 | 38.46 | 38.64 | 38.82 | 38.97 | 39.12 | 39.26 |
| JW | 37.68 | 37.71 | 37.74 | 37.80 | 37.88 | 37.96 | 38.05 | 38.15 | 38.25 | 38.34 | 38.46 |
| KW | 37.57 | 37.61 | 37.64 | 37.69 | 37.74 | 37.79 | 37.85 | 37.91 | 37.98 | 38.05 | 38.12 |
| NW | 37.61 | 37.63 | 37.67 | 37.75 | 37.84 | 37.95 | 38.06 | 38.17 | 38.27 | 38.38 | 38.49 |
| SD | 37.40 | 37.41 | 37.43 | 37.46 | 37.51 | 37.55 | 37.60 | 37.66 | 37.71 | 37.77 | 37.82 |
| SL | 37.80 | 37.81 | 37.83 | 37.86 | 37.89 | 37.93 | 37.98 | 38.03 | 38.08 | 38.15 | 38.22 |

SKIN TEMPERATURE(ºC) - PLACEBO; DAY - 2

| TIME | 0 | 10 | 20 | 30 | 40 | 50 | 60 | 70 | 80 | 90 | 100 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| BA | 32.44 | 32.43 | 32.44 | 32.44 | 32.44 | 32.42 | 32.48 | 32.60 | 32.67 | 32.63 | 32.52 |
| BM | 32.27 | 32.25 | 32.24 | 32.20 | 32.12 | 31.99 | 31.85 | 31.73 | 31.65 | 31.74 | 31.94 |
| DW | 32.43 | 32.54 | 32.58 | 32.48 | 32.37 | 32.23 | 32.12 | 32.12 | 32.26 | 32.42 | 32.42 |
| JG | 32.08 | 32.01 | 31.99 | 32.06 | 31.98 | 31.91 | 32.08 | 32.33 | 32.40 | 32.34 | 32.31 |
| JH | 32.08 | 32.02 | 31.96 | 31.84 | 31.68 | 31.48 | 31.18 | 31.14 | 31.37 | 31.73 | 31.77 |
| JW | 32.64 | 32.60 | 32.51 | 32.39 | 32.29 | 32.20 | 32.06 | 32.01 | 31.95 | 31.91 | 31.87 |
| KW | 31.56 | 31.61 | 31.61 | 31.48 | 31.33 | 31.14 | 31.52 | 31.65 | 31.30 | 31.18 | 31.18 |
| MT | 32.18 | 32.08 | 32.05 | 32.05 | 32.04 | 32.05 | 32.00 | 31.89 | 31.74 | 31.65 | 31.55 |
| NW | 32.50 | 32.48 | 32.43 | 32.38 | 32.35 | 32.22 | 32.07 | 31.37 | 31.12 | 31.44 | 31.84 |
| SD | 31.95 | 32.14 | 32.35 | 32.10 | 31.68 | 31.43 | 31.53 | 31.87 | 31.85 | 31.69 | 31.43 |
| SL | 32.76 | 32.85 | 32.90 | 32.81 | 32.65 | 32.57 | 32.47 | 32.39 | 32.34 | 32.26 | 32.23 |

SKIN TEMPERATURE(ºC) - POMS; DAY - 2

| TIME | 0 | 10 | 20 | 30 | 40 | 50 | 60 | 70 | 80 | 90 | 100 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| AW | 31.10 | 31.10 | 31.02 | 30.77 | 30.58 | 30.36 | 30.11 | 30.00 | 29.88 | 29.83 | 29.90 |
| BA | 31.51 | 31.49 | 31.45 | 31.49 | 31.55 | 31.58 | 31.62 | 31.62 | 31.67 | 31.86 | 32.11 |
| BM | 31.92 | 31.89 | 31.86 | 31.91 | 32.00 | 32.14 | 32.15 | 32.06 | 31.99 | 31.91 | 31.82 |
| DW | 32.53 | 32.70 | 32.79 | 32.77 | 32.64 | 32.46 | 32.33 | 32.32 | 32.56 | 32.85 | 32.94 |
| JG | 32.52 | 32.62 | 32.79 | 32.95 | 33.06 | 33.16 | 33.26 | 33.31 | 33.19 | 32.97 | 32.79 |
| JH | 32.27 | 32.37 | 32.22 | 32.05 | 31.85 | 31.69 | 31.51 | 31.11 | 31.12 | 31.39 | 31.39 |
| JW | 33.11 | 33.04 | 32.83 | 32.57 | 32.31 | 32.18 | 32.13 | 31.99 | 31.92 | 31.79 | 31.57 |
| KW | 31.78 | 32.20 | 32.47 | 32.23 | 31.68 | 31.32 | 31.48 | 31.84 | 32.00 | 31.96 | 31.76 |
| NW | 31.61 | 31.84 | 31.93 | 31.70 | 31.48 | 31.22 | 31.45 | 31.82 | 31.71 | 31.45 | 31.24 |
| SD | 30.84 | 30.83 | 30.74 | 30.57 | 30.60 | 30.75 | 30.88 | 30.90 | 30.83 | 30.67 | 30.54 |
| SL | 32.58 | 32.55 | 32.46 | 32.35 | 32.19 | 32.09 | 31.90 | 31.73 | 31.57 | 31.42 | 31.26 |

BODY TEMPERATURE(ºC) - PLACEBO; DAY - 2

| TIME | 0 | 10 | 20 | 30 | 40 | 50 | 60 | 70 | 80 | 90 | 100 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| BA | 37.20 | 37.20 | 37.21 | 37.22 | 37.23 | 37.25 | 37.27 | 37.31 | 37.33 | 37.34 | 37.35 |
| BM | 36.91 | 36.92 | 36.94 | 36.98 | 37.01 | 37.03 | 37.06 | 37.09 | 37.12 | 37.18 | 37.26 |
| DW | 37.03 | 37.05 | 37.09 | 37.12 | 37.16 | 37.20 | 37.25 | 37.30 | 37.39 | 37.48 | 37.54 |
| JG | 36.81 | 36.82 | 36.85 | 36.88 | 36.90 | 36.92 | 36.98 | 37.04 | 37.08 | 37.12 | 37.16 |
| JH | 37.01 | 37.06 | 37.11 | 37.18 | 37.27 | 37.37 | 37.46 | 37.60 | 37.79 | 37.97 | 38.11 |
| JW | 37.00 | 37.00 | 37.02 | 37.04 | 37.07 | 37.11 | 37.15 | 37.21 | 37.27 | 37.33 | 37.40 |
| KW | 37.07 | 37.11 | 37.14 | 37.15 | 37.16 | 37.17 | 37.25 | 37.30 | 37.30 | 37.32 | 37.37 |
| MT | 37.22 | 37.23 | 37.25 | 37.26 | 37.28 | 37.31 | 37.33 | 37.34 | 37.35 | 37.36 | 37.38 |
| NW | 36.86 | 36.88 | 36.90 | 36.95 | 36.99 | 37.03 | 37.08 | 37.06 | 37.09 | 37.21 | 37.34 |
| SD | 36.66 | 36.72 | 36.80 | 36.82 | 36.83 | 36.87 | 36.96 | 37.08 | 37.15 | 37.21 | 37.25 |
| SL | 37.27 | 37.29 | 37.32 | 37.33 | 37.33 | 37.35 | 37.38 | 37.40 | 37.44 | 37.47 | 37.52 |

BODY TEMPERATURE(ºC) - POMS; DAY - 2

| TIME | 0 | 10 | 20 | 30 | 40 | 50 | 60 | 70 | 80 | 90 | 100 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| AW | 37.04 | 37.05 | 37.06 | 37.04 | 37.04 | 37.03 | 37.02 | 37.03 | 37.04 | 37.05 | 37.09 |
| BA | 37.18 | 37.18 | 37.19 | 37.21 | 37.23 | 37.26 | 37.29 | 37.31 | 37.34 | 37.39 | 37.44 |
| BM | 37.07 | 37.09 | 37.12 | 37.16 | 37.21 | 37.26 | 37.31 | 37.35 | 37.39 | 37.44 | 37.49 |
| DW | 36.75 | 36.79 | 36.84 | 36.88 | 36.91 | 36.94 | 36.98 | 37.04 | 37.14 | 37.25 | 37.33 |
| JG | 37.23 | 37.26 | 37.30 | 37.34 | 37.38 | 37.41 | 37.45 | 37.48 | 37.49 | 37.49 | 37.50 |
| JH | 37.10 | 37.19 | 37.25 | 37.34 | 37.45 | 37.58 | 37.71 | 37.82 | 37.95 | 38.11 | 38.24 |
| JW | 37.09 | 37.10 | 37.10 | 37.12 | 37.16 | 37.21 | 37.28 | 37.35 | 37.42 | 37.49 | 37.56 |
| KW | 36.82 | 36.90 | 36.97 | 36.98 | 36.95 | 36.95 | 37.02 | 37.12 | 37.20 | 37.26 | 37.29 |
| NW | 36.83 | 36.88 | 36.93 | 36.96 | 37.02 | 37.08 | 37.20 | 37.34 | 37.42 | 37.48 | 37.54 |
| SD | 36.54 | 36.56 | 36.56 | 36.57 | 36.61 | 36.67 | 36.73 | 36.78 | 36.81 | 36.84 | 36.88 |
| SL | 37.12 | 37.12 | 37.14 | 37.14 | 37.15 | 37.17 | 37.19 | 37.21 | 37.24 | 37.28 | 37.32 |

OXYGEN SATURATION (%) - PLACEBO; DAY - 2

| TIME | 0 | 10 | 20 | 30 | 40 | 50 | 60 | 70 | 80 | 90 | 100 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| JG | 60.1 | 60.5 | 59.8 | 60.0 | 60.1 | 59.4 | 59.2 | 59.0 | 59.1 | 58.0 | 58.0 |
| JH | 53.7 | 50.7 | 49.4 | 51.0 | 51.8 | 51.7 | 54.0 | 54.6 | 53.6 | 52.9 | 53.9 |
| KW | 54.7 | 55.8 | 56.4 | 57.3 | 57.0 | 57.3 | 56.1 | 54.5 | 54.5 | 53.9 | 53.1 |
| MT | 69.8 | 68.6 | 68.2 | 69.3 | 66.8 | 66.0 | 65.2 | 65.2 | 64.9 | 65.1 | 64.3 |
| SD | 55.8 | 54.8 | 55.2 | 54.1 | 53.5 | 52.9 | 52.2 | 52.3 | 50.3 | 49.2 | 50.4 |

OXYGEN SATURATION (%) - POMS; DAY - 2

| TIME | 0 | 10 | 20 | 30 | 40 | 50 | 60 | 70 | 80 | 90 | 100 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| JG | 59.5 | 57.4 | 57.2 | 56.4 | 55.6 | 54.7 | 54.7 | 54.6 | 53.1 | 53.4 | 52.1 |
| JH | 54.3 | 53.5 | 54.4 | 55.3 | 53.2 | 51.4 | 52.3 | 52.3 | 52.1 | 52.2 | 51.4 |
| KW | 64.5 | 64.2 | 65.3 | 64.4 | 65.0 | 64.7 | 65.3 | 66.1 | 65.8 | 64.3 | 64.3 |
| MT | 69.3 | 69.7 | 69.2 | 69.5 | 69.5 | 69.5 | 69.9 | 69.7 | 68.7 | 69.0 | 68.9 |
| SD | 67.0 | 65.7 | 65.3 | 64.7 | 65.2 | 63.9 | 64.0 | 63.4 | 62.7 | 61.3 | 61.4 |

TOTAL HEMOGLOBIN CONTENT (µm) - PLACEBO; DAY - 2

| TIME | 0 | 10 | 20 | 30 | 40 | 50 | 60 | 70 | 80 | 90 | 100 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| JG | 72.6 | 72.0 | 72.1 | 71.5 | 71.8 | 72.0 | 71.2 | 71.7 | 72.6 | 71.5 | 72.0 |
| JH | 65.4 | 64.8 | 64.4 | 65.5 | 65.3 | 65.7 | 66.3 | 66.8 | 66.5 | 66.4 | 67.0 |
| KW | 58.9 | 59.3 | 59.3 | 59.4 | 59.4 | 59.5 | 58.7 | 57.7 | 58.0 | 58.7 | 60.8 |
| MT | 59.5 | 59.3 | 59.2 | 59.5 | 59.2 | 57.7 | 57.7 | 58.6 | 59.2 | 59.0 | 58.9 |
| SD | 64.5 | 64.8 | 65.8 | 64.9 | 64.9 | 65.6 | 66.0 | 65.8 | 65.5 | 65.3 | 66.3 |

TOTAL HEMOGLOBIN CONTENT (µm) - POMS; DAY - 2

| TIME | 0 | 10 | 20 | 30 | 40 | 50 | 60 | 70 | 80 | 90 | 100 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| JG | 69.6 | 68.4 | 67.9 | 68.3 | 67.6 | 66.3 | 66.9 | 66.9 | 65.2 | 64.7 | 64.9 |
| JH | 62.2 | 62.8 | 63.9 | 65.2 | 63.7 | 63.3 | 64.4 | 64.1 | 64.4 | 65.1 | 65.5 |
| KW | 67.4 | 67.5 | 69.1 | 68.7 | 69.4 | 68.8 | 68.5 | 69.1 | 69.6 | 69.9 | 70.8 |
| MT | 58.8 | 58.8 | 58.4 | 57.9 | 59.0 | 58.0 | 59.1 | 58.4 | 59.7 | 59.3 | 59.9 |
| SD | 75.6 | 74.8 | 74.7 | 74.4 | 74.6 | 73.5 | 73.6 | 74.7 | 75.2 | 74.4 | 74.7 |

OXYGENATED HEMOGLOBIN (µm) - PLACEBO; DAY - 2

| TIME | 0 | 10 | 20 | 30 | 40 | 50 | 60 | 70 | 80 | 90 | 100 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| JG | 43.6 | 43.6 | 43.1 | 42.9 | 43.2 | 42.7 | 42.2 | 42.3 | 42.9 | 41.5 | 41.7 |
| JH | 35.1 | 32.9 | 31.8 | 33.4 | 33.8 | 34.0 | 35.8 | 36.5 | 35.6 | 35.1 | 36.1 |
| KW | 32.2 | 33.1 | 33.5 | 34.1 | 33.9 | 34.1 | 33.0 | 31.4 | 31.6 | 31.6 | 32.2 |
| MT | 41.5 | 40.7 | 40.4 | 41.2 | 39.5 | 38.1 | 37.6 | 38.1 | 38.4 | 38.4 | 37.9 |
| SD | 36.0 | 35.5 | 36.3 | 35.1 | 34.7 | 34.7 | 34.4 | 34.4 | 33.0 | 32.1 | 33.4 |

OXYGENATED HEMOGLOBIN (µm) - POMS; DAY - 2

| TIME | 0 | 10 | 20 | 30 | 40 | 50 | 60 | 70 | 80 | 90 | 100 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| JG | 41.4 | 39.2 | 38.9 | 38.5 | 37.6 | 36.3 | 36.6 | 36.5 | 34.6 | 34.5 | 33.8 |
| JH | 33.7 | 33.6 | 34.7 | 36.0 | 33.9 | 32.5 | 33.7 | 33.5 | 33.5 | 33.9 | 33.7 |
| KW | 43.5 | 43.3 | 45.1 | 44.2 | 45.0 | 44.6 | 44.7 | 45.7 | 45.9 | 45.0 | 45.5 |
| MT | 40.7 | 40.9 | 40.4 | 40.3 | 41.0 | 40.3 | 41.3 | 40.7 | 41.0 | 40.9 | 41.2 |
| SD | 50.6 | 49.2 | 48.8 | 48.1 | 48.6 | 46.9 | 47.1 | 47.3 | 47.2 | 45.6 | 45.9 |

DEOXYGENATED HEMOGLOBIN (µm) - PLACEBO; DAY - 2

| TIME | 0 | 10 | 20 | 30 | 40 | 50 | 60 | 70 | 80 | 90 | 100 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| JG | 28.9 | 28.5 | 29.0 | 28.6 | 28.6 | 29.2 | 29.0 | 29.4 | 29.7 | 30.0 | 30.3 |
| JH | 30.3 | 31.9 | 32.6 | 32.1 | 31.5 | 31.7 | 30.5 | 30.3 | 30.9 | 31.3 | 30.9 |
| KW | 26.7 | 26.2 | 25.9 | 25.4 | 25.5 | 25.4 | 25.8 | 26.3 | 26.4 | 27.1 | 28.6 |
| MT | 18.0 | 18.6 | 18.8 | 18.3 | 19.7 | 19.6 | 20.1 | 20.4 | 20.8 | 20.6 | 21.0 |
| SD | 28.5 | 29.3 | 29.4 | 29.8 | 30.2 | 30.9 | 31.6 | 31.4 | 32.6 | 33.2 | 32.9 |

DEOXYGENATED HEMOGLOBIN (µm) - POMS; DAY - 2

| TIME | 0 | 10 | 20 | 30 | 40 | 50 | 60 | 70 | 80 | 90 | 100 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| JG | 28.2 | 29.2 | 29.1 | 29.8 | 30.0 | 30.0 | 30.3 | 30.4 | 30.6 | 30.1 | 31.1 |
| JH | 28.5 | 29.2 | 29.2 | 29.2 | 29.8 | 30.8 | 30.7 | 30.6 | 30.8 | 31.1 | 31.8 |
| KW | 23.9 | 24.2 | 24.0 | 24.5 | 24.3 | 24.3 | 23.8 | 23.4 | 23.8 | 24.9 | 25.3 |
| MT | 18.1 | 17.9 | 18.0 | 17.7 | 18.0 | 17.6 | 17.8 | 17.7 | 18.7 | 18.4 | 18.7 |
| SD | 25.0 | 25.6 | 25.9 | 26.3 | 26.0 | 26.6 | 26.5 | 27.4 | 28.0 | 28.8 | 28.8 |

| | TIME TO FATIGUE - DAY2 | |
|---|---|---|
| | PLACEBO (sec) | POMS (sec) |
| AW | 234 | 240 |
| BA | 226 | 250 |
| BM | 302 | 312 |
| DW | 337 | 370 |
| JG | 282 | 171 |
| JH | 533 | 597 |
| JW | 436 | 471 |
| KW | 488 | 435 |
| MT | 295 | 303 |
| NW | 478 | 550 |
| SD | 560 | 323 |
| SL | 350 | 342 |

MAXIMAL NUEROMUSCULAR POWER; DAY - 2

| | INSTANTANEOUS POWER (watts) | | MAXIMAL POWER (watts) | | REVOLUTIONS PER MINUTE | |
|---|---|---|---|---|---|---|
| Subject | PLACEBO | POMS | PLACEBO | POMS | PLACEBO | POMS |
| AW | 1840.2 | 1804.8 | 1120.8 | 1111.6 | 123.2 | 123.7 |
| BA | 1985.0 | 1847.9 | 1238.9 | 1166.3 | 118.2 | 116.4 |
| BM | 1431.2 | 1443.7 | 882.7 | 877.2 | 109.0 | 115.5 |
| DW | 1838.5 | 1681.9 | 1109.1 | 1012.2 | 110.5 | 114.7 |
| JG | 1891.2 | 1852.5 | 1131.6 | 1122.8 | 128.8 | 128.6 |
| JH | 2129.2 | 2042.6 | 1225.6 | 1200.7 | 120.9 | 104.5 |
| JW | 2114.0 | 2514.2 | 1249.9 | 1444.5 | 118.4 | 103.4 |
| KW | 2749.0 | 2868.4 | 1759.6 | 1838.9 | 107.8 | 109.6 |
| MT | 1731.7 | 1760.7 | 1104.9 | 1055.5 | 139.7 | 127.1 |
| NW | 2008.3 | 1969.1 | 1283.1 | 1223.9 | 115.5 | 121.3 |
| SD | 2385.7 | 2550.2 | 1395.5 | 1491.1 | 126.5 | 120.0 |
| SL | 2223.0 | 2212.3 | 1377.6 | 1368.5 | 116.3 | 115.9 |

**APPENDIX K**

***Individual data for study 2***

| | WORKRATE (watts) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| % VO2max | rest | 40 | 50 | 60 | 70 | 80 | 90 | 100 |
| RDS | 0 | 141 | 188 | 236 | 283 | 330 | 378 | 425 |
| AS | 0 | 135 | 178 | 222 | 265 | 308 | 352 | 395 |
| TT | 0 | 125 | 165 | 204 | 244 | 284 | 323 | 363 |
| RD | 0 | 112 | 150 | 187 | 224 | 261 | 298 | 335 |
| FC | 0 | 127 | 168 | 208 | 244 | 290 | 330 | 371 |
| DC | 0 | 158 | 205 | 252 | 300 | 346 | 393 | 440 |
| JL | 0 | 127 | 168 | 208 | 249 | 289 | 330 | 370 |
| DG | 0 | 138 | 181 | 224 | 270 | 320 | 353 | 396 |
| JH | 0 | 110 | 145 | 180 | 215 | 250 | 285 | 320 |
| TB | 0 | 144 | 189 | 235 | 280 | 325 | 370 | 415 |

| | RECTAL TEMPERATURE (ºC) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| % VO2max | rest | 40 | 50 | 60 | 70 | 80 | 90 | 100 |
| RDS | 36.87 | 37.03 | 37.34 | 37.56 | 37.75 | 37.94 | 37.99 | 37.93 |
| AS | 37.52 | 37.54 | 37.72 | 38.00 | 38.21 | 38.84 | 38.66 | 38.65 |
| TT | 37.01 | 37.03 | 37.30 | 37.54 | 37.70 | 38.22 | 38.22 | 38.28 |
| RD | 37.47 | 37.51 | 37.63 | 37.79 | 37.93 | 38.13 | 38.06 | 38.14 |
| FC | 37.36 | 37.33 | 37.54 | 37.85 | 38.07 | 38.44 | 38.46 | 38.55 |
| DC | 37.02 | 37.04 | 37.25 | 37.51 | 37.66 | 37.95 | 37.85 | 37.90 |
| JL | 37.28 | 37.29 | 37.45 | 37.64 | 37.81 | 38.03 | 37.81 | 38.01 |
| DG | 37.64 | 37.61 | 37.72 | 37.95 | 38.17 | 38.20 | 38.49 | 38.66 |
| JH | 36.94 | 36.90 | 37.01 | 37.29 | 37.53 | 38.08 | 38.08 | 38.25 |
| TB | 37.15 | 37.15 | 37.38 | 37.64 | 37.83 | 38.19 | 38.03 | 38.20 |

| | OXYGEN CONSUMPTION (l/min) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| % VO2max | rest | 40 | 50 | 60 | 70 | 80 | 90 | 100 |
| RDS | 0.422 | 2.070 | 2.510 | 3.000 | 3.444 | 4.075 | 4.456 | 4.875 |
| AS | 0.531 | 2.146 | 2.602 | 3.058 | 3.524 | 4.376 | 4.640 | 4.846 |
| TT | 0.441 | 2.192 | 2.560 | 2.896 | 3.456 | 3.784 | 4.258 | 4.580 |
| RD | 0.356 | 1.878 | 2.158 | 2.603 | 3.099 | 3.633 | 3.816 | 4.128 |
| FC | 0.382 | 1.774 | 2.186 | 2.646 | 3.059 | 3.606 | 3.974 | 4.332 |
| DC | 0.371 | 2.106 | 2.574 | 2.950 | 3.590 | 4.284 | 4.517 | 4.815 |
| JL | 0.433 | 1.912 | 2.280 | 2.665 | 3.157 | 3.672 | 4.283 | 4.415 |
| DG | 0.437 | 1.960 | 2.491 | 2.902 | 3.415 | 4.313 | 4.364 | 4.741 |
| JH | 0.380 | 1.859 | 2.201 | 2.593 | 3.002 | 3.336 | 3.581 | 3.749 |
| TB | 0.404 | 2.077 | 2.453 | 2.897 | 3.376 | 4.063 | 4.244 | 4.590 |

| | VENTILATION (l/min) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| % VO2max | rest | 40 | 50 | 60 | 70 | 80 | 90 | 100 |
| RDS | 13.5 | 47.4 | 56.5 | 67.3 | 80.1 | 105.8 | 119.9 | 138.0 |
| AS | 21.0 | 58.5 | 71.0 | 83.7 | 100.3 | 148.7 | 163.6 | 183.4 |
| TT | 17.2 | 53.6 | 63.8 | 72.6 | 90.3 | 104.5 | 127.7 | 152.0 |
| RD | 12.4 | 50.6 | 60.9 | 81.4 | 103.2 | 143.3 | 142.2 | 162.8 |
| FC | 13.5 | 41.2 | 50.0 | 61.1 | 72.2 | 92.2 | 110.8 | 133.1 |
| DC | 14.3 | 51.3 | 62.7 | 71.7 | 89.5 | 112.9 | 120.4 | 133.0 |
| JL | 13.9 | 44.0 | 52.0 | 59.1 | 70.8 | 95.4 | 130.8 | 145.2 |
| DG | 20.1 | 47.4 | 61.2 | 70.4 | 85.1 | 140.3 | 135.9 | 164.5 |
| JH | 15.9 | 47.5 | 58.1 | 69.4 | 85.9 | 108.4 | 132.0 | 146.6 |
| TB | 14.1 | 49.2 | 56.7 | 67.2 | 77.9 | 98.4 | 105.5 | 124.4 |

| | HEART RATE (bpm) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| % VO2max | rest | 40 | 50 | 60 | 70 | 80 | 90 | 100 |
| RDS | 75.2 | 122.5 | 136.7 | 149.2 | 161.6 | 173.1 | 176.9 | 183.8 |
| AS | 64.1 | 116.1 | 128.6 | 137.6 | 147.4 | 165.3 | 170.5 | 174.5 |
| TT | 53.5 | 113.0 | 128.7 | 140.7 | 157.0 | 172.2 | 180.3 | 187.4 |
| RD | 71.1 | 113.3 | 122.1 | 132.8 | 146.8 | 180.4 | 176.1 | 191.7 |
| FC | 85.2 | 130.3 | 138.3 | 148.7 | 155.2 | 168.3 | 173.8 | 180.7 |
| DC | 53.2 | 102.3 | 107.7 | 115.8 | 130.8 | 154.9 | 156.2 | 163.9 |
| JL | 73.5 | 115.0 | 124.2 | 134.3 | 147.7 | 164.7 | 173.5 | 176.3 |
| DG | 76.6 | 119.3 | 129.0 | 138.2 | 150.6 | 177.0 | 173.1 | 186.5 |
| JH | 88.0 | 127.0 | 139.5 | 147.3 | 156.8 | 169.7 | 174.8 | 179.6 |
| TB | 54.8 | 102.9 | 112.0 | 120.5 | 133.3 | 156.6 | 156.8 | 166.5 |

| | CARDIAC OUTPUT (l/min) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| % VO2max | rest | 40 | 50 | 60 | 70 | 80 | 90 | 100 |
| RDS | 7.4 | 17.9 | 20.6 | 21.8 | 23.9 | 25.2 | 27.4 | 29.3 |
| AS | 7.9 | 17.6 | 20.0 | 21.7 | 23.1 | 26.0 | 26.4 | 27.7 |
| TT | 7.1 | 15.8 | 20.0 | 20.5 | 23.9 | 24.3 | 24.3 | 26.6 |
| RD | 7.1 | 13.1 | 15.8 | 17.6 | 21.6 | 22.7 | 23.2 | 22.0 |
| FC | 9.9 | 17.4 | 19.1 | 20.9 | 22.5 | 23.7 | 24.0 | 24.6 |
| DC | 7.7 | 17.5 | 19.4 | 21.4 | 23.9 | 25.6 | 26.0 | 24.5 |
| JL | 7.8 | 14.6 | 16.3 | 17.9 | 19.7 | 21.6 | 22.9 | 23.1 |
| DG | 7.3 | 15.8 | 17.4 | 18.7 | 20.0 | 21.3 | 21.8 | 23.2 |
| JH | 6.7 | 14.8 | 16.8 | 17.9 | 19.8 | 19.7 | 20.7 | 20.6 |
| TB | 6.8 | 15.6 | 17.0 | 18.5 | 20.4 | 20.9 | 21.9 | 24.1 |

| | STROKE VOLUME (ml/beat) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| % VO2max | rest | 40 | 50 | 60 | 70 | 80 | 90 | 100 |
| RDS | 99.8 | 146.9 | 151.0 | 146.8 | 147.9 | 145.4 | 155.0 | 159.4 |
| AS | 123.7 | 151.8 | 155.3 | 157.9 | 156.9 | 157.5 | 155.0 | 158.9 |
| TT | 133.7 | 138.6 | 156.1 | 146.6 | 152.8 | 141.5 | 135.1 | 142.1 |
| RD | 99.8 | 116.5 | 129.6 | 132.9 | 147.0 | 126.0 | 131.4 | 115.1 |
| FC | 116.0 | 133.4 | 138.3 | 140.5 | 145.2 | 141.2 | 137.9 | 136.1 |
| DC | 145.5 | 171.5 | 179.8 | 184.8 | 183.0 | 165.3 | 166.7 | 149.6 |
| JL | 106.1 | 126.8 | 131.6 | 133.2 | 133.7 | 131.3 | 131.9 | 131.1 |
| DG | 95.6 | 132.4 | 134.5 | 135.4 | 133.1 | 121.2 | 126.3 | 124.5 |
| JH | 75.9 | 116.4 | 120.7 | 121.7 | 126.2 | 116.3 | 118.3 | 115.2 |
| TB | 123.8 | 151.7 | 151.4 | 153.6 | 152.7 | 133.4 | 141.1 | 144.6 |

| | ARTERIAL - VENOUS OXYGEN DIFFERENCE (ml/dl) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| % VO2max | rest | 40 | 50 | 60 | 70 | 80 | 90 | 100 |
| RDS | 5.7 | 11.5 | 12.2 | 13.8 | 14.4 | 16.2 | 16.3 | 16.5 |
| AS | 6.7 | 12.2 | 13.1 | 14.1 | 15.2 | 16.9 | 17.6 | 17.5 |
| TT | 6.2 | 14.6 | 12.8 | 14.2 | 14.5 | 15.6 | 17.6 | 17.3 |
| RD | 5.0 | 14.7 | 13.7 | 14.8 | 14.4 | 16.2 | 16.5 | 19.5 |
| FC | 3.9 | 10.2 | 11.4 | 12.7 | 13.6 | 15.3 | 16.6 | 17.6 |
| DC | 4.8 | 12.0 | 13.3 | 13.8 | 15.0 | 16.8 | 17.4 | 19.8 |
| JL | 5.6 | 13.1 | 14.0 | 14.9 | 16.0 | 17.0 | 18.8 | 19.2 |
| DG | 6.0 | 12.4 | 14.4 | 15.5 | 17.0 | 20.2 | 20.0 | 20.5 |
| JH | 5.7 | 12.6 | 13.1 | 14.5 | 15.2 | 16.9 | 17.4 | 18.3 |
| TB | 6.0 | 13.3 | 14.5 | 15.7 | 16.6 | 19.5 | 19.2 | 19.1 |

| | BASELINE DEOXYGENATED HEMOGLOBIN (μm) - VASTUS LATERALIS | | | | | | |
|---|---|---|---|---|---|---|---|
| % VO2max | 40 | 50 | 60 | 70 | 80 | 90 | 100 |
| RDS | 17.4 | 17.4 | 17.6 | 17.3 | 16.8 | 17.6 | 16.5 |
| AS | 45.0 | 44.3 | 45.2 | 45.4 | 47.8 | 46.1 | 45.6 |
| TT | 34.2 | 34.8 | 33.8 | 34.0 | 32.5 | 31.8 | 32.7 |
| RD | 40.1 | 39.4 | 40.7 | 40.2 | 42.9 | 41.3 | 42.6 |
| FC | 38.6 | 38.6 | 38.0 | 39.3 | 39.4 | 39.7 | 40.0 |
| DC | 28.0 | 27.3 | 28.0 | 28.8 | 27.8 | 28.2 | 27.8 |
| JL | 35.3 | 34.9 | 35.9 | 35.0 | 37.8 | 38.6 | 38.2 |
| JH | 44.5 | 43.3 | 44.0 | 46.2 | 48.4 | 48.5 | 49.5 |
| TB | 37.0 | 37.0 | 37.3 | 36.6 | 39.6 | 37.6 | 38.9 |

| | NORMALIZED DEOXYGENATED HEMOGLOBIN (%) - VASTUS LATERALIS | | | | | | |
|---|---|---|---|---|---|---|---|
| % VO2max | 40 | 50 | 60 | 70 | 80 | 90 | 100 |
| RDS | 42.1 | 47.8 | 69.3 | 90.6 | 94.7 | 81.7 | 100.0 |
| AS | 19.7 | 33.4 | 51.6 | 71.7 | 85.8 | 100.0 | 99.7 |
| TT | 27.8 | 45.7 | 69.2 | 82.7 | 90.9 | 100.0 | 90.4 |
| RD | 26.6 | 48.4 | 55.8 | 80.6 | 86.9 | 94.5 | 100.0 |
| FC | 46.1 | 50.3 | 71.2 | 80.7 | 95.7 | 93.2 | 100.0 |
| DC | 35.5 | 52.7 | 65.9 | 56.3 | 76.2 | 81.8 | 100.0 |
| JL | 37.0 | 55.0 | 70.1 | 89.5 | 89.8 | 100.0 | 97.0 |
| JH | 14.6 | 28.9 | 45.6 | 63.1 | 82.6 | 93.6 | 100.0 |
| TB | 29.8 | 47.5 | 60.6 | 78.4 | 85.9 | 100.0 | 70.4 |

| | NORMALIZED CAPILLARY BLOOD FLOW (%) - VASTUS LATERALIS | | | | | | |
|---|---|---|---|---|---|---|---|
| % VO2max | 40 | 50 | 60 | 70 | 80 | 90 | 100 |
| RDS | 51.5 | 61.2 | 67.8 | 72.7 | 85.0 | 96.8 | 100.0 |
| AS | 60.4 | 68.9 | 75.2 | 80.2 | 94.7 | 95.6 | 100.0 |
| TT | 60.6 | 65.8 | 68.1 | 77.5 | 82.5 | 90.1 | 100.0 |
| RD | 63.6 | 65.3 | 76.1 | 81.2 | 92.7 | 94.5 | 100.0 |
| FC | 50.1 | 60.6 | 67.6 | 75.5 | 84.5 | 93.9 | 100.0 |
| DC | 58.1 | 65.0 | 70.1 | 89.2 | 97.1 | 100.0 | 98.9 |
| JL | 56.2 | 61.5 | 67.3 | 73.6 | 85.5 | 95.9 | 100.0 |
| JH | 71.2 | 78.6 | 85.7 | 92.2 | 94.9 | 97.7 | 100.0 |
| TB | 54.7 | 59.2 | 65.9 | 71.1 | 83.1 | 82.1 | 100.0 |

| | BASELINE DEOXYGENATED HEMOGLOBIN (μm) - GASTROCNEMIUS | | | | | | |
|---|---|---|---|---|---|---|---|
| % VO2max | 40 | 50 | 60 | 70 | 80 | 90 | 100 |
| RDS | 7.2 | 7.2 | 7.5 | 7.4 | 7.2 | 6.9 | 7.3 |
| AS | 26.1 | 25.7 | 26.8 | 25.7 | 29.7 | 28.2 | 27.5 |
| TT | 11.5 | 11.3 | 11.6 | 11.4 | 11.4 | 11.6 | 10.9 |
| RD | 23.7 | 23.7 | 23.5 | 23.9 | 24.1 | 24.1 | 24.3 |
| FC | 30.8 | 31.1 | 30.5 | 30.7 | 33.3 | 34.2 | 33.9 |
| DC | 16.1 | 16.4 | 15.8 | 16.2 | 18.1 | 16.8 | 16.6 |
| JL | 14.6 | 14.3 | 14.5 | 15.0 | 16.9 | 18.2 | 16.8 |
| JH | 21.3 | 20.9 | 21.4 | 21.6 | 23.1 | 23.8 | 22.2 |
| TB | 18.9 | 17.8 | 19.5 | 19.3 | 23.5 | 21.4 | 18.1 |

| | NORMALIZED DEOXYGENATED HEMOGLOBIN (%) - GASTROCNEMIUS | | | | | | |
|---|---|---|---|---|---|---|---|
| % VO2max | 40 | 50 | 60 | 70 | 80 | 90 | 100 |
| RDS | 27.0 | 71.9 | 63.2 | 81.8 | 95.2 | 100.0 | 86.1 |
| AS | 53.4 | 56.6 | 75.6 | 94.2 | 75.7 | 95.4 | 100.0 |
| TT | 40.5 | 38.9 | 52.4 | 71.3 | 79.5 | 83.2 | 100.0 |
| RD | 44.3 | 44.1 | 57.0 | 58.8 | 81.5 | 86.0 | 100.0 |
| FC | 47.1 | 43.1 | 60.1 | 86.9 | 89.3 | 84.1 | 100.0 |
| DC | 59.7 | 53.4 | 71.6 | 73.0 | 94.6 | 89.3 | 100.0 |
| JL | 53.7 | 58.2 | 60.9 | 67.6 | 67.8 | 78.9 | 100.0 |
| JH | 43.1 | 58.0 | 65.8 | 71.4 | 72.4 | 73.4 | 100.0 |
| TB | 2.6 | 56.8 | 53.0 | 76.6 | 84.7 | 97.6 | 100.0 |

| | NORMALIZED DEOXYGENATED HEMOGLOBIN (%) - GASTROCNEMIUS | | | | | | |
|---|---|---|---|---|---|---|---|
| % VO2max | 40 | 50 | 60 | 70 | 80 | 90 | 100 |
| RDS | 52.2 | 53.9 | 66.3 | 71.6 | 81.3 | 87.6 | 100.0 |
| AS | 52.4 | 62.8 | 68.7 | 74.1 | 98.3 | 97.2 | 100.0 |
| TT | 59.4 | 69.8 | 74.9 | 83.3 | 88.5 | 98.4 | 100.0 |
| RD | 58.0 | 66.7 | 75.7 | 89.3 | 94.8 | 97.7 | 100.0 |
| FC | 49.8 | 62.5 | 70.6 | 73.9 | 86.4 | 96.9 | 100.0 |
| DC | 52.1 | 65.5 | 69.0 | 83.5 | 90.9 | 97.9 | 100.0 |
| JL | 49.8 | 58.2 | 67.2 | 77.3 | 89.9 | 100.0 | 94.8 |
| JH | 58.9 | 65.4 | 74.6 | 84.5 | 93.5 | 100.0 | 94.8 |
| TB | 71.5 | 63.8 | 76.7 | 80.7 | 93.9 | 93.3 | 100.0 |

**APPENDIX L**

***Individual data for study 3***

HEART RATE (bpm)

| Subject | Normothermia + Placebo | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| TIME | 0 | 5 | 10 | 15 | 20 | 30 | 40 | 50 | 60 |
| AP | 68.0 | 132.4 | 138.0 | 137.8 | 145.1 | 142.6 | 143.1 | 146.6 | 154.3 |
| AT | 83.5 | 142.2 | 162.3 | 162.9 | 164.2 | 168.6 | 170.8 | 171.2 | 172.6 |
| CC | 77.7 | 146.6 | 154.1 | 155.1 | 156.1 | 157.1 | 161.8 | 159.9 | 163.6 |
| DD | 62.0 | 111.1 | 120.2 | 123.2 | 122.3 | 131.0 | 135.9 | 136.8 | 137.4 |
| JC | 68.1 | 115.6 | 121.7 | 127.8 | 125.6 | 134.0 | 137.2 | 139.3 | 142.7 |
| JK | 63.8 | 123.4 | 130.4 | 133.5 | 137.3 | 140.5 | 140.7 | 142.6 | 144.0 |
| JM | 80.8 | 134.7 | 142.0 | 144.6 | 148.8 | 152.5 | 153.7 | 160.3 | 161.4 |
| JR | 75.3 | 128.5 | 138.4 | 143.7 | 148.0 | 152.2 | 157.0 | 159.1 | 160.0 |
| MC | 69.1 | 135.6 | 148.1 | 152.8 | 155.0 | 159.0 | 161.3 | 162.7 | 163.2 |
| TT | 77.3 | 137.2 | 142.6 | 144.5 | 146.9 | 150.1 | 154.3 | 155.6 | 156.9 |
| NY | 75.1 | 123.8 | 130.1 | 132.5 | 134.6 | 137.0 | 140.1 | 142.8 | 144.6 |

| | Normothermia + Beta Blockade | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| TIME | 0 | 5 | 10 | 15 | 20 | 30 | 40 | 50 | 60 |
| AP | 65.2 | 129.7 | 131.7 | 129.9 | 127.0 | 131.2 | 129.8 | 131.9 | 130.0 |
| AT | 86.6 | 153.0 | 159.0 | 159.3 | 160.4 | 154.5 | 156.8 | 157.2 | 156.9 |
| CC | 75.0 | 143.8 | 147.1 | 147.3 | 146.2 | 144.7 | 144.0 | 142.4 | 141.6 |
| DD | 63.7 | 112.2 | 116.7 | 117.2 | 114.6 | 112.3 | 113.9 | 114.5 | 113.8 |
| JC | 66.0 | 122.5 | 127.4 | 130.5 | 129.1 | 128.8 | 130.8 | 131.0 | 134.7 |
| JK | 67.9 | 129.5 | 135.6 | 133.6 | 130.9 | 130.7 | 128.5 | 129.8 | 128.3 |
| JM | 81.4 | 130.1 | 136.9 | 139.1 | 139.2 | 138.6 | 137.9 | 140.6 | 140.0 |
| JR | 63.8 | 116.1 | 125.0 | 125.6 | 125.4 | 125.7 | 123.6 | 123.3 | 124.7 |
| MC | 65.1 | 133.0 | 139.2 | 143.2 | 137.5 | 139.5 | 135.3 | 132.9 | 134.4 |
| TT | 72.7 | 137.1 | 142.5 | 142.3 | 143.5 | 150.7 | 150.0 | 149.4 | 152.3 |
| NY | 73.1 | 128.0 | 129.9 | 129.8 | 131.9 | 128.1 | 134.6 | 132.3 | 131.7 |

| | Hyperthermia + Placebo | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| TIME | 0 | 5 | 10 | 15 | 20 | 30 | 40 | 50 | 60 |
| AP | 68.2 | 130.3 | 138.5 | 143.6 | 150.8 | 155.7 | 160.3 | 165.0 | 171.8 |
| AT | 84.1 | 155.3 | 167.8 | 175.2 | 178.2 | 185.8 | 190.9 | 194.5 | 197.6 |
| CC | 85.3 | 153.4 | 164.4 | 168.1 | 171.7 | 174.7 | 181.7 | 183.0 | 183.8 |
| DD | 65.5 | 115.3 | 129.8 | 135.0 | 142.8 | 150.3 | 159.9 | 163.8 | 166.3 |
| JC | 74.4 | 123.5 | 138.3 | 144.5 | 153.0 | 159.0 | 171.1 | 175.9 | 182.9 |
| JK | 82.1 | 134.2 | 150.6 | 154.5 | 158.7 | 161.5 | 168.8 | 174.8 | 176.7 |
| JM | 80.7 | 138.2 | 152.4 | 160.8 | 163.9 | 177.3 | 184.1 | 188.3 | 193.4 |
| JR | 69.6 | 141.8 | 150.7 | 156.6 | 158.7 | 166.7 | 169.4 | 172.4 | 173.9 |
| MC | 69.0 | 134.3 | 149.8 | 153.3 | 156.2 | 166.9 | 171.4 | 176.5 | 177.0 |
| TT | 82.3 | 144.9 | 156.1 | 155.9 | 162.3 | 173.5 | 170.5 | 171.5 | 175.6 |
| NY | 76.4 | 134.5 | 142.5 | 150.5 | 155.7 | 168.4 | 171.6 | 179.5 | 182.5 |

| | Hyperthermia + Beta Blockade | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| TIME | 0 | 5 | 10 | 15 | 20 | 30 | 40 | 50 | 60 |
| AP | 68.9 | 130.5 | 135.7 | 133.8 | 135.2 | 135.2 | 137.1 | 140.5 | 143.3 |
| AT | 89.1 | 166.7 | 171.2 | 171.2 | 170.5 | 173.0 | 174.4 | 172.0 | 178.3 |
| CC | 85.0 | 152.5 | 163.3 | 165.3 | 166.9 | 164.3 | 166.2 | 164.5 | 164.9 |
| DD | 72.0 | 117.3 | 126.0 | 126.4 | 127.6 | 130.0 | 127.5 | 131.5 | 133.2 |
| JC | 70.0 | 125.0 | 140.6 | 142.3 | 142.9 | 145.8 | 154.5 | 155.6 | 159.4 |
| JK | 78.3 | 132.4 | 143.4 | 144.1 | 144.4 | 140.8 | 143.4 | 145.6 | 149.2 |
| JM | 81.6 | 136.6 | 146.8 | 153.4 | 154.1 | 154.5 | 160.5 | 159.4 | 159.7 |
| JR | 63.8 | 122.7 | 128.4 | 130.0 | 135.1 | 140.0 | 136.8 | 139.6 | 140.1 |
| MC | 66.1 | 136.6 | 147.4 | 150.0 | 152.6 | 152.7 | 146.7 | 144.6 | 147.3 |
| TT | 77.1 | 143.3 | 146.9 | 149.7 | 153.7 | 159.1 | 156.0 | 166.9 | 167.4 |
| NY | 77.5 | 127.2 | 134.8 | 138.2 | 141.4 | 139.7 | 142.9 | 149.1 | 149.1 |

STROKE VOLUME (ml/beat)

| Subject | Normothermia + Placebo | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| TIME | 0 | 5 | 10 | 15 | 20 | 30 | 40 | 50 | 60 |
| AP | 90.4 | 135.2 | 141.7 | 136.2 | 141.2 | 140.6 | 132.4 | 135.5 | 122.8 |
| AT | 94.1 | 129.5 | 114.2 | 122.3 | 121.5 | 113.7 | 107.6 | 108.0 | 111.9 |
| CC | 103.3 | 124.7 | 120.0 | 121.1 | 117.8 | 123.4 | 113.4 | 121.5 | 119.5 |
| DD | 95.2 | 150.6 | 143.2 | 132.5 | 139.3 | 135.7 | 126.3 | 125.3 | 116.9 |
| JC | 104.9 | 160.3 | 164.6 | 153.3 | 154.9 | 151.5 | 152.9 | 148.5 | 146.1 |
| JK | 111.2 | 131.0 | 123.7 | 114.2 | 114.8 | 115.4 | 120.7 | 125.4 | 110.8 |
| JM | 75.3 | 108.8 | 110.7 | 108.9 | 107.6 | 105.1 | 101.4 | 97.0 | 96.2 |
| JR | 99.1 | 150.4 | 140.2 | 143.5 | 141.0 | 137.8 | 133.1 | 138.3 | 136.1 |
| MC | 133.3 | 168.5 | 152.6 | 144.4 | 147.7 | 146.0 | 143.0 | 141.3 | 140.5 |
| TT | 88.2 | 144.1 | 130.8 | 137.9 | 136.8 | 136.2 | 132.4 | 130.1 | 129.3 |
| NY | 72.5 | 134.9 | 141.7 | 132.7 | 124.6 | 128.3 | 124.6 | 128.8 | 123.6 |

| | Normothermia + Beta Blockade | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| TIME | 0 | 5 | 10 | 15 | 20 | 30 | 40 | 50 | 60 |
| AP | 96.0 | 134.4 | 133.0 | 127.1 | 142.9 | 131.1 | 144.7 | 131.4 | 124.3 |
| AT | 85.6 | 124.8 | 113.3 | 123.1 | 116.8 | 131.1 | 118.7 | 115.8 | 128.3 |
| CC | 114.0 | 137.7 | 132.7 | 131.6 | 132.8 | 136.9 | 141.5 | 145.5 | 142.8 |
| DD | 87.7 | 137.8 | 127.8 | 144.0 | 130.9 | 133.2 | 138.2 | 129.7 | 125.9 |
| JC | 103.7 | 146.2 | 146.5 | 133.5 | 146.5 | 149.5 | 149.7 | 159.5 | 158.3 |
| JK | 97.9 | 125.2 | 114.2 | 121.9 | 120.7 | 119.0 | 124.8 | 128.8 | 130.4 |
| JM | 78.3 | 130.3 | 125.6 | 117.4 | 126.0 | 127.7 | 116.6 | 118.3 | 117.9 |
| JR | 99.4 | 160.0 | 166.2 | 165.6 | 168.0 | 179.5 | 175.6 | 167.0 | 178.7 |
| MC | 142.8 | 159.3 | 143.9 | 146.2 | 161.4 | 168.3 | 162.2 | 163.2 | 175.6 |
| TT | 98.8 | 144.7 | 140.9 | 129.9 | 131.8 | 134.9 | 142.9 | 142.7 | 124.3 |
| NY | 82.0 | 132.5 | 133.9 | 135.5 | 130.3 | 145.3 | 123.8 | 133.7 | 130.1 |

| | Hyperthermia + Placebo | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| TIME | 0 | 5 | 10 | 15 | 20 | 30 | 40 | 50 | 60 |
| AP | 92.2 | 133.6 | 128.1 | 139.7 | 125.9 | 115.8 | 122.6 | 124.3 | 107.0 |
| AT | 90.9 | 120.0 | 114.8 | 112.8 | 102.3 | 104.5 | 104.0 | 102.9 | 91.3 |
| CC | 95.9 | 122.2 | 120.2 | 115.5 | 118.8 | 122.1 | 117.4 | 120.8 | 118.5 |
| DD | 96.5 | 142.7 | 134.2 | 126.7 | 126.2 | 115.0 | 107.1 | 104.2 | 97.0 |
| JC | 94.7 | 164.0 | 143.1 | 145.2 | 129.5 | 138.6 | 130.6 | 125.8 | 125.3 |
| JK | 89.0 | 115.5 | 118.5 | 111.3 | 116.4 | 113.3 | 107.8 | 101.8 | 101.4 |
| JM | 78.3 | 125.2 | 113.6 | 112.9 | 102.6 | 101.5 | 101.2 | 93.6 | 95.7 |
| JR | 95.2 | 145.8 | 145.5 | 142.6 | 144.8 | 139.5 | 135.7 | 130.4 | 126.8 |
| MC | 129.6 | 165.9 | 156.4 | 146.3 | 146.9 | 139.7 | 146.0 | 143.3 | 130.5 |
| TT | 87.1 | 156.3 | 116.3 | 125.5 | 121.6 | 108.6 | 121.2 | 116.5 | 123.5 |
| NY | 81.7 | 139.4 | 122.0 | 126.8 | 122.0 | 111.2 | 108.2 | 105.2 | 102.0 |

| | Hyperthermia + Beta Blockade | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| TIME | 0 | 5 | 10 | 15 | 20 | 30 | 40 | 50 | 60 |
| AP | 97.0 | 134.0 | 139.0 | 141.5 | 142.1 | 152.8 | 148.0 | 148.4 | 141.5 |
| AT | 92.3 | 118.0 | 105.0 | 125.6 | 118.8 | 119.0 | 116.9 | 119.4 | 122.3 |
| CC | 96.9 | 122.9 | 130.1 | 128.4 | 126.2 | 125.7 | 123.2 | 134.9 | 130.6 |
| DD | 96.4 | 128.3 | 120.8 | 139.3 | 125.9 | 135.4 | 144.0 | 129.2 | 120.7 |
| JC | 97.7 | 158.4 | 141.5 | 142.2 | 135.3 | 143.4 | 137.5 | 139.8 | 134.2 |
| JK | 94.3 | 131.6 | 126.9 | 128.5 | 132.2 | 129.1 | 135.7 | 130.1 | 126.6 |
| JM | 73.3 | 101.4 | 94.6 | 93.2 | 95.4 | 101.9 | 94.8 | 95.6 | 99.8 |
| JR | 111.3 | 196.8 | 167.1 | 175.7 | 166.6 | 162.9 | 163.7 | 172.2 | 177.5 |
| MC | 144.2 | 158.0 | 164.4 | 161.1 | 154.9 | 166.8 | 160.4 | 175.8 | 160.2 |
| TT | 91.4 | 134.8 | 122.3 | 129.6 | 124.8 | 125.2 | 122.2 | 115.3 | 115.6 |
| NY | 78.7 | 143.0 | 139.9 | 144.0 | 140.2 | 134.6 | 128.9 | 128.9 | 124.5 |

CARDIAC OUTPUT (l/min)

| Subject | Normothermia + Placebo | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| TIME | 0 | 5 | 10 | 15 | 20 | 30 | 40 | 50 | 60 |
| AP | 6.2 | 17.9 | 19.6 | 18.8 | 20.5 | 20.1 | 19.0 | 19.9 | 19.0 |
| AT | 7.9 | 18.4 | 18.5 | 19.9 | 20.0 | 19.2 | 18.4 | 18.5 | 19.3 |
| CC | 8.0 | 18.3 | 18.5 | 18.8 | 18.4 | 19.4 | 18.4 | 19.4 | 19.5 |
| DD | 5.9 | 16.7 | 17.2 | 16.3 | 17.0 | 17.8 | 17.2 | 17.2 | 16.1 |
| JC | 7.1 | 18.5 | 20.0 | 19.6 | 19.5 | 20.3 | 21.0 | 20.7 | 20.8 |
| JK | 7.1 | 16.2 | 16.1 | 15.3 | 15.8 | 16.2 | 17.0 | 17.9 | 16.0 |
| JM | 6.1 | 14.7 | 15.7 | 15.8 | 16.0 | 16.0 | 15.6 | 15.6 | 15.5 |
| JR | 7.5 | 19.3 | 19.4 | 20.6 | 20.9 | 21.0 | 20.9 | 22.0 | 21.8 |
| MC | 9.2 | 22.9 | 22.6 | 22.1 | 22.9 | 23.2 | 23.1 | 23.0 | 22.9 |
| TT | 6.8 | 19.8 | 18.7 | 19.9 | 20.1 | 20.4 | 20.4 | 20.2 | 20.3 |
| NY | 5.4 | 16.7 | 18.4 | 17.6 | 16.8 | 17.6 | 17.5 | 18.4 | 17.9 |

| | Normothermia + Beta Blockade | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| TIME | 0 | 5 | 10 | 15 | 20 | 30 | 40 | 50 | 60 |
| AP | 6.3 | 17.4 | 17.5 | 16.5 | 18.2 | 17.2 | 18.8 | 17.3 | 16.2 |
| AT | 7.4 | 19.1 | 18.0 | 19.6 | 18.7 | 20.3 | 18.6 | 18.2 | 20.1 |
| CC | 8.6 | 19.8 | 19.5 | 19.4 | 19.4 | 19.8 | 20.4 | 20.7 | 20.2 |
| DD | 5.6 | 15.5 | 14.9 | 16.9 | 15.0 | 15.0 | 15.7 | 14.9 | 14.3 |
| JC | 6.8 | 17.9 | 18.7 | 17.4 | 18.9 | 19.3 | 19.6 | 20.9 | 21.3 |
| JK | 6.6 | 16.2 | 15.5 | 16.3 | 15.8 | 15.6 | 16.0 | 16.7 | 16.7 |
| JM | 6.4 | 16.9 | 17.2 | 16.3 | 17.5 | 17.7 | 16.1 | 16.6 | 16.5 |
| JR | 6.3 | 18.6 | 20.8 | 20.8 | 21.1 | 22.6 | 21.7 | 20.6 | 22.3 |
| MC | 9.3 | 21.2 | 20.0 | 20.9 | 22.2 | 23.5 | 22.0 | 21.7 | 23.6 |
| TT | 7.1 | 19.8 | 20.1 | 18.5 | 18.9 | 20.3 | 21.4 | 21.3 | 18.9 |
| NY | 6.0 | 17.0 | 17.4 | 17.6 | 17.2 | 18.6 | 16.7 | 17.7 | 17.1 |

| | Hyperthermia + Placebo | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| TIME | 0 | 5 | 10 | 15 | 20 | 30 | 40 | 50 | 60 |
| AP | 6.3 | 17.4 | 17.7 | 20.1 | 19.0 | 18.0 | 19.7 | 20.5 | 18.4 |
| AT | 7.7 | 18.6 | 19.3 | 19.8 | 18.2 | 19.4 | 19.9 | 20.0 | 18.0 |
| CC | 8.2 | 18.8 | 19.8 | 19.4 | 20.4 | 21.3 | 21.3 | 22.1 | 21.8 |
| DD | 6.3 | 16.5 | 17.4 | 17.1 | 18.0 | 17.3 | 17.1 | 17.1 | 16.1 |
| JC | 7.1 | 20.3 | 19.8 | 21.0 | 19.8 | 22.0 | 22.4 | 22.1 | 22.9 |
| JK | 7.3 | 15.5 | 17.9 | 17.2 | 18.5 | 18.3 | 18.2 | 17.8 | 17.9 |
| JM | 6.3 | 17.3 | 17.3 | 18.2 | 16.8 | 18.0 | 18.6 | 17.6 | 18.5 |
| JR | 6.6 | 20.7 | 21.9 | 22.3 | 23.0 | 23.2 | 23.0 | 22.5 | 22.1 |
| MC | 8.9 | 22.3 | 23.4 | 22.4 | 22.9 | 23.3 | 25.0 | 25.3 | 23.1 |
| TT | 7.2 | 22.6 | 18.2 | 19.6 | 19.7 | 18.8 | 20.7 | 20.0 | 21.7 |
| NY | 6.2 | 18.8 | 17.4 | 19.1 | 19.0 | 18.7 | 18.6 | 18.9 | 18.6 |

| | Hyperthermia + Beta Blockade | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| TIME | 0 | 5 | 10 | 15 | 20 | 30 | 40 | 50 | 60 |
| AP | 6.7 | 17.5 | 18.9 | 18.9 | 19.2 | 20.7 | 20.3 | 20.9 | 20.3 |
| AT | 8.2 | 19.7 | 18.0 | 21.5 | 20.3 | 20.6 | 20.4 | 20.5 | 21.8 |
| CC | 8.2 | 18.7 | 21.2 | 21.2 | 21.1 | 20.7 | 20.5 | 22.2 | 21.6 |
| DD | 6.9 | 15.0 | 15.2 | 17.6 | 16.1 | 17.6 | 18.4 | 17.0 | 16.1 |
| JC | 6.8 | 19.8 | 19.9 | 20.2 | 19.3 | 20.9 | 21.2 | 21.8 | 21.4 |
| JK | 7.4 | 17.4 | 18.2 | 18.5 | 19.1 | 18.2 | 19.5 | 19.0 | 18.9 |
| JM | 6.0 | 15.0 | 15.4 | 15.9 | 15.2 | 15.6 | 15.5 | 16.2 | 16.4 |
| JR | 7.1 | 24.2 | 21.5 | 22.8 | 22.5 | 22.8 | 22.4 | 24.0 | 24.9 |
| MC | 9.5 | 21.6 | 24.2 | 24.2 | 23.6 | 25.5 | 23.5 | 25.4 | 23.6 |
| TT | 7.0 | 19.3 | 18.0 | 19.4 | 19.2 | 19.9 | 19.1 | 19.2 | 19.4 |
| NY | 6.1 | 18.2 | 18.9 | 19.9 | 19.8 | 18.8 | 18.4 | 19.2 | 18.6 |

TOTAL PERIPHERAL RESISTANCE (pru)

| Subject | Normothermia + Placebo | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| TIME | 0 | 5 | 10 | 15 | 20 | 30 | 40 | 50 | 60 |
| AP | 14.14 | 6.09 | 5.88 | 5.33 | 5.01 | 5.03 | 5.31 | 5.22 | 5.11 |
| AT | 13.08 | 6.08 | 5.77 | 5.57 | 5.89 | 5.79 | 6.22 | 6.25 | 5.86 |
| CC | 12.19 | 5.29 | 5.20 | 5.35 | 5.31 | 4.56 | 4.72 | 5.14 | 4.72 |
| DD | 13.26 | 6.34 | 6.93 | 6.52 | 6.35 | 6.05 | 5.90 | 5.76 | 6.60 |
| JC | 12.55 | 5.16 | 4.89 | 4.72 | 5.05 | 4.69 | 4.97 | 5.13 | 4.72 |
| JK | 13.57 | 6.45 | 7.12 | 6.79 | 6.43 | 6.41 | 5.71 | 5.56 | 5.55 |
| JM | 17.73 | 7.83 | 7.45 | 6.77 | 7.31 | 7.23 | 6.87 | 6.89 | 6.53 |
| JR | 13.24 | 6.92 | 5.72 | 5.36 | 5.55 | 5.14 | 5.20 | 5.75 | 5.23 |
| MC | 9.71 | 5.01 | 4.76 | 4.92 | 4.82 | 4.45 | 4.75 | 4.97 | 4.43 |
| TT | 14.20 | 5.66 | 5.81 | 5.19 | 5.51 | 5.69 | 5.05 | 5.24 | 4.72 |
| NY | 15.73 | 5.98 | 6.07 | 6.23 | 5.94 | 5.49 | 5.59 | 5.86 | 5.30 |

| | Normothermia + Beta Blockade | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| TIME | 0 | 5 | 10 | 15 | 20 | 30 | 40 | 50 | 60 |
| AP | 13.74 | 5.81 | 5.71 | 5.86 | 5.45 | 5.48 | 4.92 | 5.67 | 5.61 |
| AT | 13.73 | 6.40 | 5.92 | 5.94 | 5.85 | 5.65 | 6.20 | 6.22 | 5.34 |
| CC | 11.97 | 5.23 | 5.25 | 5.34 | 5.20 | 4.91 | 4.48 | 4.62 | 4.22 |
| DD | 16.17 | 6.66 | 6.97 | 6.68 | 6.92 | 6.36 | 6.02 | 6.42 | 6.11 |
| JC | 14.34 | 5.73 | 5.69 | 6.22 | 5.73 | 5.42 | 5.37 | 4.70 | 4.57 |
| JK | 14.29 | 7.33 | 7.98 | 6.85 | 7.22 | 6.84 | 6.45 | 6.54 | 6.11 |
| JM | 16.70 | 6.83 | 6.99 | 7.34 | 6.90 | 6.17 | 6.29 | 6.30 | 6.06 |
| JR | 17.24 | 6.41 | 6.02 | 6.00 | 5.51 | 5.21 | 4.98 | 4.83 | 4.59 |
| MC | 10.83 | 5.22 | 6.18 | 5.92 | 5.70 | 5.70 | 5.55 | 5.37 | 5.78 |
| TT | 12.16 | 5.45 | 4.90 | 5.22 | 5.42 | 4.61 | 4.15 | 4.83 | 4.77 |
| NY | 15.21 | 6.00 | 6.36 | 5.69 | 5.62 | 5.69 | 6.11 | 5.92 | 6.31 |

| | Hyperthermia + Placebo | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| TIME | 0 | 5 | 10 | 15 | 20 | 30 | 40 | 50 | 60 |
| AP | 14.14 | 6.09 | 5.88 | 5.33 | 5.01 | 5.03 | 5.31 | 5.22 | 5.11 |
| AT | 12.66 | 6.06 | 4.79 | 5.09 | 5.66 | 4.92 | 5.23 | 4.35 | 5.37 |
| CC | 12.07 | 5.19 | 5.38 | 5.20 | 5.30 | 5.42 | 4.41 | 4.37 | 4.36 |
| DD | 15.34 | 6.55 | 5.87 | 5.84 | 6.00 | 5.42 | 5.69 | 5.57 | 5.90 |
| JC | 13.61 | 4.64 | 4.43 | 4.21 | 4.36 | 3.94 | 3.84 | 3.95 | 3.81 |
| JK | 13.12 | 6.57 | 6.29 | 5.87 | 5.81 | 5.52 | 5.24 | 5.90 | 5.39 |
| JM | 14.81 | 5.97 | 5.96 | 5.51 | 6.09 | 5.48 | 5.25 | 5.35 | 5.19 |
| JR | 14.80 | 5.28 | 5.45 | 5.02 | 4.54 | 4.94 | 4.74 | 4.60 | 4.55 |
| MC | 10.52 | 4.83 | 5.02 | 4.75 | 4.59 | 4.56 | 4.16 | 4.38 | 4.09 |
| TT | 13.56 | 4.94 | 5.62 | 5.31 | 5.40 | 5.12 | 4.45 | 4.50 | 4.50 |
| NY | 14.80 | 5.51 | 6.31 | 5.83 | 5.91 | 5.59 | 5.24 | 5.19 | 4.90 |

| | Hyperthermia + Beta Blockade | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| TIME | 0 | 5 | 10 | 15 | 20 | 30 | 40 | 50 | 60 |
| AP | 12.72 | 5.41 | 4.92 | 5.05 | 5.12 | 4.41 | 4.73 | 5.33 | 4.62 |
| AT | 11.77 | 5.18 | 5.98 | 4.99 | 5.40 | 4.94 | 4.98 | 4.92 | 4.66 |
| CC | 12.65 | 4.85 | 4.83 | 4.88 | 4.62 | 4.32 | 4.46 | 4.35 | 4.19 |
| DD | 12.05 | 6.71 | 6.30 | 5.83 | 5.51 | 5.65 | 5.70 | 5.64 | 5.94 |
| JC | 13.49 | 4.73 | 4.70 | 4.45 | 4.56 | 3.85 | 3.88 | 3.91 | 3.73 |
| JK | 13.56 | 6.27 | 5.96 | 5.47 | 5.50 | 5.85 | 5.09 | 5.05 | 5.06 |
| JM | 16.51 | 7.54 | 7.12 | 6.88 | 6.75 | 6.38 | 6.18 | 5.05 | 5.47 |
| JR | 12.81 | 4.48 | 5.35 | 4.97 | 7.26 | 4.81 | 4.42 | 3.90 | 3.89 |
| MC | 10.31 | 4.73 | 4.46 | 4.20 | 4.35 | 4.13 | 4.15 | 4.12 | 4.26 |
| TT | 13.59 | 5.10 | 5.28 | 5.15 | 4.94 | 4.65 | 4.74 | 4.27 | 4.16 |
| NY | 14.70 | 5.02 | 5.27 | 5.06 | 5.08 | 5.75 | 6.18 | 5.53 | 5.08 |

BODY TEMPERATURE (ºc)

| Subject | Normothermia + Placebo | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| TIME | 0 | 5 | 10 | 15 | 20 | 30 | 40 | 50 | 60 |
| AP | 35.80 | 35.74 | 36.01 | 36.37 | 36.56 | 36.87 | 37.00 | 37.09 | 37.22 |
| AT | 36.40 | 36.34 | 36.55 | 36.65 | 36.77 | 36.88 | 36.97 | 37.13 | 37.12 |
| CC | 36.67 | 36.62 | 36.90 | 37.10 | 37.18 | 37.29 | 37.34 | 37.39 | 37.47 |
| DD | 35.83 | 35.82 | 35.96 | 36.17 | 36.30 | 36.50 | 36.60 | 36.62 | 36.63 |
| JC | 36.23 | 36.20 | 36.27 | 36.50 | 36.62 | 36.83 | 36.97 | 36.99 | 37.07 |
| JK | 36.50 | 36.50 | 36.82 | 37.17 | 37.40 | 37.65 | 37.76 | 37.79 | 37.80 |
| JM | 36.35 | 36.35 | 36.48 | 36.67 | 36.75 | 36.94 | 37.08 | 37.14 | 37.26 |
| MC | 36.12 | 36.06 | 36.22 | 36.47 | 36.52 | 36.71 | 36.84 | 36.91 | 37.03 |
| TT | 36.18 | 36.13 | 36.30 | 36.55 | 36.81 | 37.22 | 37.46 | 37.69 | 37.82 |
| JR | 36.12 | 36.05 | 36.10 | 36.36 | 36.43 | 36.64 | 36.76 | 36.85 | 36.88 |
| NY | 36.47 | 36.34 | 36.38 | 36.56 | 36.69 | 36.90 | 37.02 | 37.07 | 37.15 |

| | Normothermia + Beta Blockade | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| TIME | 0 | 5 | 10 | 15 | 20 | 30 | 40 | 50 | 60 |
| AP | 35.72 | 35.80 | 36.13 | 36.47 | 36.60 | 36.85 | 36.98 | 37.05 | 37.28 |
| AT | 36.42 | 36.33 | 36.38 | 36.53 | 36.63 | 36.79 | 37.02 | 37.12 | 37.33 |
| CC | 36.56 | 36.58 | 36.86 | 37.04 | 37.06 | 37.26 | 37.34 | 37.36 | 37.36 |
| DD | 35.75 | 35.75 | 35.90 | 36.11 | 36.24 | 36.51 | 36.63 | 36.70 | 36.81 |
| JC | 36.28 | 36.20 | 36.34 | 36.56 | 36.64 | 36.84 | 37.00 | 37.14 | 37.31 |
| JK | 36.59 | 36.57 | 36.74 | 36.96 | 37.15 | 37.40 | 37.58 | 37.69 | 37.77 |
| JM | 36.26 | 36.22 | 36.35 | 36.55 | 36.62 | 36.81 | 36.91 | 37.02 | 37.14 |
| MC | 36.09 | 35.95 | 36.10 | 36.39 | 36.46 | 36.70 | 36.86 | 36.92 | 37.02 |
| TT | 35.72 | 35.69 | 35.90 | 36.20 | 36.48 | 36.83 | 37.09 | 37.26 | 37.44 |
| JR | 35.91 | 35.92 | 36.04 | 36.24 | 36.35 | 36.57 | 36.82 | 36.99 | 37.15 |
| NY | 36.39 | 36.33 | 36.37 | 36.54 | 36.71 | 36.94 | 37.09 | 37.19 | 37.33 |

| | Hyperthermia + Placebo | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| TIME | 0 | 5 | 10 | 15 | 20 | 30 | 40 | 50 | 60 |
| AP | 36.45 | 36.49 | 36.57 | 36.74 | 36.95 | 37.35 | 37.77 | 38.13 | 38.36 |
| AT | 37.13 | 37.28 | 37.46 | 37.64 | 37.81 | 38.11 | 38.39 | 38.70 | 38.98 |
| CC | 37.14 | 37.23 | 37.35 | 37.48 | 37.63 | 37.93 | 38.20 | 38.40 | 38.62 |
| DD | 36.11 | 36.15 | 36.48 | 36.59 | 36.72 | 36.96 | 37.20 | 37.39 | 37.59 |
| JC | 36.69 | 36.72 | 36.96 | 37.15 | 37.33 | 37.73 | 37.99 | 38.33 | 38.68 |
| JK | 37.23 | 37.35 | 37.64 | 37.77 | 37.88 | 38.19 | 38.51 | 38.79 | 39.06 |
| JM | 36.82 | 36.83 | 36.92 | 37.03 | 37.13 | 37.38 | 37.72 | 38.06 | 38.44 |
| MC | 36.73 | 36.67 | 36.76 | 36.87 | 36.99 | 37.14 | 37.41 | 37.68 | 38.00 |
| TT | 36.54 | 36.63 | 37.06 | 37.41 | 37.69 | 38.16 | 38.73 | 39.11 | 39.11 |
| JR | 36.55 | 36.69 | 36.92 | 37.00 | 37.19 | 37.51 | 37.88 | 38.28 | 38.63 |
| NY | 36.79 | 36.76 | 36.99 | 37.19 | 37.34 | 37.67 | 38.00 | 38.27 | 38.54 |

| | Hyperthermia + Beta Blockade | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| TIME | 0 | 5 | 10 | 15 | 20 | 30 | 40 | 50 | 60 |
| AP | 36.29 | 36.40 | 36.65 | 36.93 | 37.18 | 37.67 | 38.04 | 38.26 | 38.44 |
| AT | 37.23 | 37.27 | 37.37 | 37.49 | 37.65 | 37.90 | 38.16 | 38.57 | 38.94 |
| CC | 37.26 | 37.31 | 37.47 | 37.56 | 37.70 | 37.95 | 38.26 | 38.43 | 38.69 |
| DD | 36.50 | 36.48 | 36.63 | 36.71 | 36.83 | 37.09 | 37.33 | 37.53 | 37.70 |
| JC | 36.77 | 36.75 | 36.81 | 36.89 | 37.03 | 37.26 | 37.54 | 37.95 | 38.36 |
| JK | 37.23 | 37.39 | 37.79 | 37.95 | 38.01 | 38.28 | 38.51 | 38.72 | 38.93 |
| JM | 36.66 | 36.69 | 36.79 | 36.89 | 37.00 | 37.25 | 37.56 | 37.77 | 38.04 |
| MC | 36.71 | 36.67 | 36.75 | 36.82 | 36.86 | 37.10 | 37.39 | 37.68 | 37.97 |
| TT | 36.32 | 36.38 | 36.77 | 37.09 | 37.38 | 37.79 | 38.24 | 38.60 | 38.99 |
| JR | 36.93 | 36.87 | 36.98 | 37.01 | 37.16 | 37.36 | 37.62 | 37.95 | 38.33 |
| NY | 37.09 | 37.04 | 37.06 | 37.17 | 37.27 | 37.53 | 37.81 | 38.04 | 38.31 |

CORE TEMPERATURE (ºC)

| Subject | Normothermia + Placebo | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| TIME | 0 | 5 | 10 | 15 | 20 | 30 | 40 | 50 | 60 |
| AP | 36.70 | 36.68 | 36.95 | 37.20 | 37.38 | 37.67 | 37.82 | 37.94 | 38.03 |
| AT | 37.16 | 37.09 | 37.21 | 37.28 | 37.45 | 37.60 | 37.69 | 37.95 | 37.97 |
| CC | 37.40 | 37.43 | 37.68 | 37.86 | 37.99 | 38.15 | 38.21 | 38.30 | 38.34 |
| DD | 36.66 | 36.66 | 36.75 | 36.89 | 37.00 | 37.21 | 37.34 | 37.42 | 37.40 |
| JC | 37.04 | 37.06 | 37.12 | 37.27 | 37.42 | 37.68 | 37.87 | 37.98 | 38.06 |
| JK | 37.31 | 37.34 | 37.62 | 37.97 | 38.18 | 38.44 | 38.57 | 38.62 | 38.64 |
| JM | 37.16 | 37.18 | 37.26 | 37.37 | 37.49 | 37.70 | 37.85 | 37.95 | 38.06 |
| JR | 36.99 | 36.97 | 36.99 | 37.18 | 37.26 | 37.51 | 37.63 | 37.75 | 37.76 |
| MC | 37.07 | 37.07 | 37.17 | 37.27 | 37.37 | 37.58 | 37.78 | 37.94 | 38.06 |
| TT | 36.91 | 36.94 | 37.09 | 37.34 | 37.60 | 38.02 | 38.29 | 38.54 | 38.67 |
| NY | 37.23 | 37.18 | 37.21 | 37.33 | 37.43 | 37.64 | 37.77 | 37.87 | 37.89 |

| | Normothermia + Beta Blockade | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| TIME | 0 | 5 | 10 | 15 | 20 | 30 | 40 | 50 | 60 |
| AP | 36.53 | 36.69 | 37.05 | 37.28 | 37.40 | 37.68 | 37.87 | 37.92 | 38.11 |
| AT | 37.16 | 37.12 | 37.08 | 37.22 | 37.35 | 37.54 | 37.80 | 38.04 | 38.19 |
| CC | 37.36 | 37.44 | 37.69 | 37.87 | 38.00 | 38.18 | 38.29 | 38.37 | 38.44 |
| DD | 36.57 | 36.59 | 36.70 | 36.84 | 36.99 | 37.26 | 37.41 | 37.51 | 37.59 |
| JC | 37.12 | 37.06 | 37.17 | 37.31 | 37.44 | 37.71 | 37.93 | 38.12 | 38.26 |
| JK | 37.44 | 37.46 | 37.59 | 37.81 | 38.01 | 38.29 | 38.47 | 38.60 | 38.69 |
| JM | 37.10 | 37.10 | 37.18 | 37.31 | 37.41 | 37.61 | 37.77 | 37.90 | 37.99 |
| JR | 36.77 | 36.81 | 36.89 | 37.01 | 37.13 | 37.39 | 37.64 | 37.84 | 38.00 |
| MC | 37.02 | 36.91 | 37.00 | 37.13 | 37.27 | 37.53 | 37.80 | 37.93 | 38.01 |
| TT | 36.49 | 36.55 | 36.72 | 37.02 | 37.27 | 37.60 | 37.89 | 38.11 | 38.26 |
| NY | 37.27 | 37.23 | 37.27 | 37.41 | 37.53 | 37.75 | 37.91 | 38.04 | 38.16 |

| | Hyperthermia + Placebo | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| TIME | 0 | 5 | 10 | 15 | 20 | 30 | 40 | 50 | 60 |
| AP | 36.80 | 36.81 | 36.89 | 37.05 | 37.23 | 37.63 | 38.06 | 38.51 | 38.86 |
| AT | 37.38 | 37.47 | 37.64 | 37.90 | 38.10 | 38.48 | 38.80 | 39.22 | 39.52 |
| CC | 37.42 | 37.45 | 37.58 | 37.74 | 37.89 | 38.22 | 38.53 | 38.83 | 39.12 |
| DD | 36.31 | 36.34 | 36.57 | 36.73 | 36.86 | 37.12 | 37.35 | 37.59 | 37.85 |
| JC | 36.97 | 36.98 | 37.18 | 37.38 | 37.58 | 38.03 | 38.37 | 38.75 | 39.07 |
| JK | 37.45 | 37.44 | 37.63 | 37.84 | 38.04 | 38.44 | 38.78 | 39.10 | 39.40 |
| JM | 37.01 | 37.03 | 37.08 | 37.16 | 37.26 | 37.53 | 37.87 | 38.25 | 38.67 |
| JR | 36.99 | 37.02 | 37.12 | 37.24 | 37.40 | 37.76 | 38.16 | 38.59 | 39.01 |
| MC | 37.13 | 37.10 | 37.14 | 37.22 | 37.31 | 37.57 | 37.86 | 38.16 | 38.46 |
| TT | 36.78 | 36.84 | 37.21 | 37.59 | 37.91 | 38.44 | 39.04 | 39.46 | 39.48 |
| NY | 37.10 | 37.06 | 37.23 | 37.43 | 37.59 | 37.92 | 38.24 | 38.59 | 38.92 |

| | Hyperthermia + Beta Blockade | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| TIME | 0 | 5 | 10 | 15 | 20 | 30 | 40 | 50 | 60 |
| AP | 36.73 | 36.83 | 37.05 | 37.30 | 37.53 | 38.07 | 38.45 | 38.73 | 38.99 |
| AT | 37.49 | 37.46 | 37.57 | 37.73 | 37.93 | 38.33 | 38.70 | 39.15 | 39.51 |
| CC | 37.43 | 37.45 | 37.61 | 37.77 | 37.92 | 38.23 | 38.56 | 38.89 | 39.22 |
| DD | 36.77 | 36.71 | 36.76 | 36.88 | 37.02 | 37.29 | 37.54 | 37.83 | 38.01 |
| JC | 37.04 | 37.02 | 37.04 | 37.11 | 37.23 | 37.52 | 37.88 | 38.30 | 38.73 |
| JK | 37.40 | 37.47 | 37.82 | 38.08 | 38.24 | 38.54 | 38.79 | 39.04 | 39.30 |
| JM | 36.94 | 36.96 | 37.01 | 37.09 | 37.21 | 37.50 | 37.81 | 38.14 | 38.45 |
| JR | 37.12 | 37.10 | 37.13 | 37.21 | 37.32 | 37.60 | 37.93 | 38.34 | 38.67 |
| MC | 37.14 | 37.11 | 37.15 | 37.22 | 37.32 | 37.61 | 37.93 | 38.23 | 38.54 |
| TT | 36.58 | 36.62 | 36.93 | 37.27 | 37.57 | 38.01 | 38.47 | 38.84 | 39.29 |
| NY | 37.29 | 37.28 | 37.30 | 37.39 | 37.51 | 37.80 | 38.08 | 38.42 | 38.77 |

SKIN TEMPERATURE (ºc)

| Subject | Normothermia + Placebo | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| TIME | 0 | 5 | 10 | 15 | 20 | 30 | 40 | 50 | 60 |
| AP | 29.82 | 29.47 | 29.70 | 30.81 | 31.07 | 31.54 | 31.50 | 31.43 | 31.74 |
| AT | 31.34 | 31.31 | 32.13 | 32.43 | 32.23 | 32.11 | 32.14 | 31.65 | 31.44 |
| CC | 31.79 | 31.19 | 31.69 | 32.00 | 31.72 | 31.54 | 31.55 | 31.34 | 31.66 |
| DD | 30.29 | 30.19 | 30.66 | 31.33 | 31.59 | 31.73 | 31.61 | 31.30 | 31.41 |
| JC | 30.79 | 30.46 | 30.59 | 31.38 | 31.33 | 31.14 | 30.92 | 30.35 | 30.41 |
| JK | 31.07 | 30.94 | 31.50 | 31.85 | 32.16 | 32.31 | 32.30 | 32.20 | 32.20 |
| JM | 30.96 | 30.77 | 31.32 | 31.96 | 31.80 | 31.83 | 31.88 | 31.68 | 31.88 |
| JR | 30.31 | 29.86 | 30.14 | 30.82 | 30.88 | 30.83 | 30.93 | 30.81 | 30.97 |
| MC | 29.71 | 29.31 | 29.85 | 31.11 | 30.81 | 30.85 | 30.54 | 29.97 | 30.12 |
| TT | 31.32 | 30.72 | 31.00 | 31.26 | 31.49 | 31.86 | 31.90 | 32.05 | 32.14 |
| NY | 31.42 | 30.70 | 30.79 | 31.40 | 31.70 | 31.97 | 31.99 | 31.68 | 32.25 |

| | Normothermia + Beta Blockade | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| TIME | 0 | 5 | 10 | 15 | 20 | 30 | 40 | 50 | 60 |
| AP | 30.34 | 29.81 | 29.99 | 31.00 | 31.21 | 31.31 | 31.04 | 31.28 | 31.71 |
| AT | 31.41 | 31.05 | 31.75 | 31.94 | 31.82 | 31.79 | 31.86 | 31.00 | 31.61 |
| CC | 31.24 | 30.88 | 31.32 | 31.43 | 30.79 | 31.10 | 31.01 | 30.56 | 30.08 |
| DD | 30.30 | 30.11 | 30.53 | 31.19 | 31.26 | 31.49 | 31.41 | 31.32 | 31.61 |
| JC | 30.70 | 30.39 | 30.73 | 31.54 | 31.23 | 31.07 | 30.72 | 30.61 | 30.96 |
| JK | 30.88 | 30.66 | 31.01 | 31.25 | 31.38 | 31.50 | 31.63 | 31.54 | 31.57 |
| JM | 30.66 | 30.27 | 30.74 | 31.44 | 31.31 | 31.45 | 31.10 | 31.17 | 31.47 |
| JR | 30.13 | 30.00 | 30.32 | 31.08 | 31.12 | 31.08 | 31.34 | 31.29 | 31.46 |
| MC | 29.85 | 29.57 | 30.12 | 31.40 | 31.10 | 31.11 | 30.59 | 30.20 | 30.35 |
| TT | 30.54 | 29.96 | 30.36 | 30.76 | 31.25 | 31.67 | 31.75 | 31.64 | 31.92 |
| NY | 30.54 | 30.27 | 30.32 | 30.74 | 31.24 | 31.54 | 31.64 | 31.50 | 31.79 |

| | Hyperthermia + Placebo | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| TIME | 0 | 5 | 10 | 15 | 20 | 30 | 40 | 50 | 60 |
| AP | 34.04 | 34.36 | 34.42 | 34.67 | 35.04 | 35.46 | 35.86 | 35.59 | 34.97 |
| AT | 35.48 | 36.06 | 36.23 | 35.87 | 35.85 | 35.60 | 35.64 | 35.20 | 35.34 |
| CC | 35.32 | 35.78 | 35.76 | 35.73 | 35.86 | 35.98 | 35.99 | 35.46 | 35.26 |
| DD | 34.75 | 34.90 | 35.81 | 35.63 | 35.83 | 35.92 | 36.24 | 36.07 | 35.88 |
| JC | 34.86 | 35.00 | 35.48 | 35.60 | 35.65 | 35.73 | 35.42 | 35.51 | 36.08 |
| JK | 35.77 | 36.70 | 37.73 | 37.31 | 36.80 | 36.50 | 36.74 | 36.71 | 36.76 |
| JM | 35.59 | 35.46 | 35.87 | 36.18 | 36.24 | 36.36 | 36.68 | 36.79 | 36.86 |
| JR | 33.63 | 34.45 | 35.58 | 35.36 | 35.76 | 35.81 | 35.97 | 36.24 | 36.15 |
| MC | 34.10 | 33.77 | 34.23 | 34.52 | 34.81 | 34.29 | 34.39 | 34.46 | 34.95 |
| TT | 34.93 | 35.24 | 36.07 | 36.15 | 36.23 | 36.34 | 36.61 | 36.76 | 36.76 |
| NY | 34.66 | 34.74 | 35.35 | 35.62 | 35.70 | 36.00 | 36.40 | 36.18 | 36.00 |

| | Hyperthermia + Beta Blockade | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| TIME | 0 | 5 | 10 | 15 | 20 | 30 | 40 | 50 | 60 |
| AP | 33.35 | 33.50 | 33.98 | 34.43 | 34.84 | 35.02 | 35.29 | 35.13 | 34.78 |
| AT | 35.52 | 35.95 | 36.05 | 35.89 | 35.76 | 35.01 | 34.56 | 34.69 | 35.11 |
| CC | 36.10 | 36.33 | 36.49 | 36.20 | 36.20 | 36.05 | 36.26 | 35.31 | 35.08 |
| DD | 34.67 | 34.92 | 35.74 | 35.55 | 35.56 | 35.74 | 35.94 | 35.48 | 35.57 |
| JC | 34.99 | 34.96 | 35.23 | 35.41 | 35.71 | 35.54 | 35.23 | 35.57 | 35.89 |
| JK | 36.09 | 36.83 | 37.63 | 37.11 | 36.46 | 36.59 | 36.65 | 36.60 | 36.43 |
| JM | 34.77 | 34.84 | 35.30 | 35.52 | 35.57 | 35.55 | 35.94 | 35.26 | 35.35 |
| JR | 35.64 | 35.36 | 35.96 | 35.69 | 36.06 | 35.76 | 35.59 | 35.31 | 36.05 |
| MC | 33.79 | 33.66 | 34.08 | 34.14 | 33.80 | 33.68 | 33.81 | 33.99 | 34.22 |
| TT | 34.55 | 34.78 | 35.72 | 35.89 | 36.10 | 36.33 | 36.69 | 36.94 | 36.97 |
| NY | 35.79 | 35.42 | 35.42 | 35.70 | 35.63 | 35.79 | 35.95 | 35.50 | 35.20 |

SYSTOLIC BLOOD PRESSURE (mmHg)

| Subject | Normothermia + Placebo | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| TIME | 0 | 5 | 10 | 15 | 20 | 30 | 40 | 50 | 60 |
| AP | 125 | 168.5 | 176.5 | 173.5 | 167 | 162.5 | 158 | 167 | 168 |
| AT | 138.5 | 188 | 196 | 199 | 204 | 200.5 | 209 | 207.5 | 207 |
| CC | 130.5 | 160 | 179 | 188.5 | 178.5 | 175.5 | 191 | 187.5 | 190.5 |
| DD | 126 | 170 | 201.5 | 196.5 | 198.5 | 204 | 194.5 | 189 | 191 |
| JC | 126 | 164.5 | 174 | 162.5 | 171.5 | 169 | 174 | 179 | 179 |
| JK | 128 | 166.5 | 198 | 191 | 193 | 187 | 187 | 185 | 181.5 |
| JM | 134.5 | 180 | 191.5 | 190 | 193 | 190.5 | 183.5 | 190.5 | 179 |
| MC | 118.5 | 166 | 178.5 | 180.5 | 186.5 | 182.5 | 188.5 | 188.5 | 180 |
| TT | 124.5 | 170 | 166 | 171.5 | 163 | 182 | 174 | 174.5 | 160 |
| JR | 133.5 | 171.5 | 156 | 204 | 192.5 | 194 | 198.5 | 182 | 202 |
| NY | 109 | 153 | 161.5 | 166.5 | 162 | 159.5 | 156.5 | 163 | 158.5 |

| | Normothermia + Beta Blockade | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| TIME | 0 | 5 | 10 | 15 | 20 | 30 | 40 | 50 | 60 |
| AP | 114 | 147 | 152 | 148.5 | 144.5 | 144.5 | 140.5 | 147.5 | 141 |
| AT | 136.5 | 181 | 189.5 | 200 | 195 | 192.5 | 198 | 193.5 | 188 |
| CC | 139 | 183 | 185 | 193.5 | 196 | 182 | 183 | 179.5 | 171 |
| DD | 120 | 166.5 | 180 | 177 | 168.5 | 168 | 165 | 160 | 159.5 |
| JC | 126.5 | 165 | 173 | 181.5 | 180.5 | 178 | 170 | 175 | 170.5 |
| JK | 129 | 180 | 211 | 195.5 | 192 | 196 | 185 | 189.5 | 186 |
| JM | 134.5 | 186.5 | 189 | 195.5 | 198 | 183 | 164 | 163.5 | 163.5 |
| MC | 139 | 179 | 193.5 | 194.5 | 187.5 | 185 | 188 | 178.5 | 184 |
| TT | 111 | 156 | 142 | 169 | 173.5 | 154.5 | 158.5 | 166 | 160 |
| JR | 142 | 178.5 | 211 | 215.5 | 204 | 205 | 189.5 | 186.5 | 175.5 |
| NY | 110.5 | 153.5 | 168.5 | 156 | 163 | 157.5 | 155.5 | 156.5 | 162 |

| | Hyperthermia + Placebo | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| TIME | 0 | 5 | 10 | 15 | 20 | 30 | 40 | 50 | 60 |
| AP | 113.5 | 153 | 150.5 | 146 | 162 | 170 | 153.5 | 157 | 154.5 |
| AT | 135.5 | 182 | 176 | 199.5 | 200.5 | 198 | 205 | 182 | 197 |
| CC | 138 | 181 | 197.5 | 196 | 195 | 205.5 | 193 | 186.5 | 188 |
| DD | 128 | 173 | 178.5 | 185.5 | 194 | 179.5 | 182 | 182.5 | 186 |
| JC | 122 | 167 | 175 | 178.5 | 174.5 | 183 | 182 | 174.5 | 176 |
| JK | 134.5 | 182.5 | 191 | 188 | 194.5 | 194.5 | 189 | 197.5 | 188 |
| JM | 128.5 | 170 | 182.5 | 185.5 | 187 | 181.5 | 180 | 179.5 | 176 |
| MC | 125 | 146.5 | 182 | 182 | 187.5 | 190.5 | 194 | 192 | 185 |
| TT | 132 | 167.5 | 165 | 167 | 169 | 165.5 | 177.5 | 177 | 177 |
| JR | 145 | 196.5 | 214 | 220.5 | 203.5 | 207 | 225 | 190 | 197.5 |
| NY | 116 | 160 | 162.5 | 163.5 | 163.5 | 155.5 | 157.5 | 157.5 | 158 |

| | Hyperthermia + Beta Blockade | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| TIME | 0 | 5 | 10 | 15 | 20 | 30 | 40 | 50 | 60 |
| AP | 117 | 145.5 | 144.5 | 144.5 | 154 | 138.5 | 148 | 155.5 | 146.5 |
| AT | 133.5 | 173 | 205 | 196 | 207.5 | 206.5 | 201 | 201.5 | 193 |
| CC | 142.5 | 171.5 | 189.5 | 188.5 | 193 | 194 | 189 | 188.5 | 183.5 |
| DD | 124 | 163.5 | 186 | 182 | 187 | 193 | 178 | 172 | 170.5 |
| JC | 125.5 | 164 | 179 | 176 | 180.5 | 167.5 | 170 | 178 | 168.5 |
| JK | 133.5 | 185.5 | 186 | 185.5 | 190.5 | 196.5 | 185.5 | 195.5 | 183 |
| JM | 132.5 | 176 | 180.5 | 178.5 | 176 | 177 | 170.5 | 154.5 | 165 |
| MC | 132 | 169 | 170.5 | 175.5 | 175.5 | 178 | 178.5 | 178 | 173 |
| TT | 127 | 159 | 161.5 | 174 | 173 | 167.5 | 168.5 | 162 | 152.5 |
| JR | 128 | 174 | 194 | 192 | 200.5 | 201 | 196 | 186.5 | 197.5 |
| NY | 108 | 159.5 | 157.5 | 158.5 | 158.5 | 159 | 151 | 156 | 173 |

DIASTOLIC BLOOD PRESSURE (mmHg)

| Subject | Normothermia + Placebo | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| TIME | 0 | 5 | 10 | 15 | 20 | 30 | 40 | 50 | 60 |
| AP | 68.0 | 78.0 | 81.0 | 66.5 | 68.0 | 67.0 | 73.5 | 71.5 | 67.5 |
| AT | 85.0 | 69.0 | 62.5 | 65.0 | 69.5 | 73.5 | 67.5 | 70.5 | 62.5 |
| CC | 81.5 | 70.0 | 61.0 | 58.5 | 57.5 | 44.0 | 46.0 | 58.0 | 45.0 |
| DD | 54.5 | 64.5 | 63.0 | 68.5 | 61.0 | 60.0 | 65.0 | 67.0 | 62.5 |
| JC | 71.5 | 68.5 | 67.5 | 64.0 | 67.0 | 66.5 | 73.5 | 72.0 | 63.0 |
| JK | 80.5 | 70.5 | 74.0 | 62.0 | 64.0 | 65.5 | 56.5 | 56.0 | 58.0 |
| JM | 94.5 | 88.5 | 80.0 | 74.0 | 79.0 | 78.5 | 69.0 | 75.5 | 70.5 |
| MC | 75.0 | 87.0 | 72.0 | 71.5 | 69.5 | 57.0 | 65.0 | 62.5 | 60.5 |
| TT | 83.0 | 88.0 | 79.5 | 73.5 | 84.0 | 84.0 | 72.5 | 75.5 | 60.0 |
| JR | 81.5 | 93.5 | 94.5 | 68.0 | 73.0 | 68.5 | 69.0 | 74.0 | 73.0 |
| NY | 74.0 | 74.5 | 77.5 | 76.0 | 73.5 | 70.5 | 76.0 | 78.5 | 69.0 |

| | Normothermia + Beta Blockade | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| TIME | 0 | 5 | 10 | 15 | 20 | 30 | 40 | 50 | 60 |
| AP | 72.0 | 79.5 | 74.0 | 72.0 | 73.0 | 69.0 | 66.5 | 75.0 | 71.0 |
| AT | 84.5 | 90.0 | 74.0 | 77.5 | 75.5 | 73.0 | 76.0 | 76.0 | 71.5 |
| CC | 84.0 | 57.5 | 56.5 | 53.5 | 51.5 | 48.5 | 41.0 | 47.5 | 39.5 |
| DD | 75.5 | 72.0 | 71.0 | 76.0 | 67.0 | 61.0 | 64.0 | 63.0 | 58.5 |
| JC | 84.0 | 76.5 | 82.0 | 86.0 | 73.0 | 73.0 | 77.5 | 64.5 | 62.0 |
| JK | 78.0 | 88.0 | 85.5 | 77.0 | 77.0 | 68.0 | 68.5 | 71.5 | 66.5 |
| JM | 92.5 | 79.5 | 82.5 | 82.0 | 76.5 | 74.0 | 74.5 | 76.0 | 72.0 |
| MC | 81.5 | 81.5 | 96.5 | 97.0 | 92.0 | 101.5 | 89.5 | 88.0 | 90.5 |
| TT | 74.0 | 90.0 | 89.0 | 71.5 | 63.5 | 72.0 | 58.0 | 71.5 | 55.5 |
| JR | 93.0 | 89.5 | 80.0 | 80.5 | 74.5 | 71.0 | 69.5 | 54.0 | 63.5 |
| NY | 81.5 | 82.5 | 86.5 | 83.0 | 79.0 | 82.5 | 84.0 | 82.0 | 87.0 |

| | Hyperthermia + Placebo | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| TIME | 0 | 5 | 10 | 15 | 20 | 30 | 40 | 50 | 60 |
| AP | 69.5 | 70.5 | 69.5 | 58.0 | 56.5 | 53.0 | 51.0 | 49.5 | 59.5 |
| AT | 77.5 | 76.5 | 48.0 | 52.0 | 56.5 | 51.0 | 52.0 | 48.0 | 51.5 |
| CC | 79.0 | 53.5 | 55.0 | 54.5 | 61.0 | 71.0 | 46.0 | 47.5 | 45.0 |
| DD | 81.5 | 64.0 | 64.0 | 54.0 | 59.5 | 50.0 | 54.0 | 53.5 | 52.5 |
| JC | 83.0 | 63.5 | 50.0 | 48.5 | 50.5 | 41.0 | 40.5 | 51.0 | 48.0 |
| JK | 76.5 | 69.5 | 72.5 | 59.5 | 67.0 | 58.0 | 55.5 | 59.5 | 61.0 |
| JM | 76.0 | 69.0 | 69.5 | 69.0 | 70.0 | 63.0 | 61.0 | 59.5 | 53.5 |
| MC | 78.5 | 86.5 | 77.5 | 67.5 | 66.0 | 63.0 | 51.0 | 53.5 | 42.5 |
| TT | 80.5 | 79.0 | 77.0 | 78.5 | 80.0 | 72.5 | 51.0 | 54.5 | 54.5 |
| JR | 74.5 | 66.0 | 71.0 | 58.5 | 53.0 | 63.0 | 50.5 | 49.5 | 52.5 |
| NY | 80.5 | 80.0 | 85.0 | 84.0 | 84.5 | 74.0 | 73.5 | 68.0 | 65.0 |

| | Hyperthermia + Beta Blockade | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| TIME | 0 | 5 | 10 | 15 | 20 | 30 | 40 | 50 | 60 |
| AP | 69.0 | 73.5 | 70.5 | 73.0 | 70.5 | 66.0 | 69.5 | 65.0 | 58.5 |
| AT | 78.5 | 65.0 | 63.0 | 61.0 | 62.0 | 53.0 | 51.0 | 55.0 | 51.5 |
| CC | 85.0 | 49.5 | 50.5 | 53.5 | 46.5 | 35.0 | 42.5 | 47.0 | 42.5 |
| DD | 63.5 | 63.0 | 53.5 | 58.5 | 57.0 | 54.0 | 55.5 | 57.5 | 58.0 |
| JC | 75.5 | 64.0 | 56.5 | 52.5 | 51.5 | 45.5 | 43.0 | 43.0 | 43.0 |
| JK | 83.5 | 75.5 | 72.0 | 61.5 | 63.0 | 64.5 | 60.0 | 49.5 | 54.0 |
| JM | 82.0 | 82.0 | 74.0 | 74.5 | 73.0 | 66.5 | 65.5 | 55.0 | 60.5 |
| MC | 81.5 | 70.5 | 72.0 | 69.5 | 66.0 | 66.5 | 58.0 | 60.0 | 61.0 |
| TT | 80.0 | 80.5 | 62.5 | 67.5 | 63.5 | 58.5 | 56.5 | 50.5 | 43.5 |
| JR | 72.5 | 75.5 | 78.5 | 73.5 | 73.5 | 64.5 | 53.0 | 47.5 | 43.0 |
| NY | 80.5 | 60.5 | 71.0 | 71.0 | 74.0 | 88.0 | 94.0 | 80.0 | 76.0 |

MEAN ARTERIAL BLOOD PRESSURE (mmHg)

| Subject | Normothermia + Placebo | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| TIME | 0 | 5 | 10 | 15 | 20 | 30 | 40 | 50 | 60 |
| AP | 87.0 | 108.2 | 112.8 | 102.2 | 101.0 | 98.8 | 101.7 | 103.3 | 101.0 |
| AT | 102.8 | 108.7 | 107.0 | 109.7 | 114.3 | 115.8 | 114.7 | 116.2 | 110.7 |
| CC | 97.8 | 100.0 | 100.3 | 101.8 | 97.8 | 87.8 | 94.3 | 101.2 | 93.5 |
| DD | 78.3 | 99.7 | 109.2 | 111.2 | 106.8 | 108.0 | 108.2 | 107.7 | 105.3 |
| JC | 89.7 | 100.5 | 103.0 | 100.8 | 101.8 | 100.7 | 107.0 | 107.7 | 101.7 |
| JK | 96.3 | 102.5 | 115.3 | 105.0 | 107.0 | 106.0 | 100.0 | 99.0 | 99.2 |
| JM | 107.8 | 119.0 | 117.2 | 112.7 | 117.0 | 115.8 | 107.2 | 113.8 | 106.7 |
| JR | 98.8 | 119.5 | 115.0 | 113.3 | 112.8 | 110.3 | 112.2 | 110.0 | 116.0 |
| MC | 89.5 | 113.3 | 107.5 | 107.8 | 108.5 | 98.8 | 106.2 | 104.5 | 100.3 |
| TT | 96.8 | 115.3 | 108.3 | 106.2 | 110.3 | 116.7 | 106.3 | 108.5 | 93.3 |
| NY | 85.7 | 100.7 | 105.5 | 106.2 | 103.0 | 100.2 | 102.8 | 106.7 | 98.8 |

| | Normothermia + Beta Blockade | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| TIME | 0 | 5 | 10 | 15 | 20 | 30 | 40 | 50 | 60 |
| AP | 86.0 | 102.0 | 100.0 | 97.5 | 96.8 | 94.2 | 91.2 | 99.2 | 94.3 |
| AT | 101.8 | 120.3 | 112.5 | 118.3 | 115.3 | 112.8 | 116.7 | 115.2 | 110.3 |
| CC | 102.3 | 99.3 | 99.3 | 100.2 | 99.7 | 93.0 | 88.3 | 91.5 | 83.3 |
| DD | 90.3 | 103.5 | 107.3 | 109.7 | 100.8 | 96.7 | 97.7 | 95.3 | 92.2 |
| JC | 98.2 | 106.0 | 112.3 | 111.2 | 108.8 | 108.0 | 108.3 | 101.3 | 98.2 |
| JK | 95.0 | 118.7 | 127.3 | 116.5 | 115.3 | 110.7 | 107.3 | 110.8 | 106.3 |
| JM | 106.5 | 115.2 | 118.0 | 119.8 | 117.0 | 110.3 | 104.3 | 105.2 | 102.5 |
| JR | 98.0 | 119.3 | 119.3 | 123.4 | 120.3 | 114.6 | 110.3 | 104.1 | 103.5 |
| MC | 100.7 | 114.0 | 128.8 | 129.5 | 123.8 | 129.3 | 122.3 | 118.2 | 121.7 |
| TT | 86.3 | 112.0 | 106.7 | 104.0 | 100.2 | 99.5 | 91.5 | 103.0 | 90.3 |
| NY | 91.2 | 106.2 | 113.8 | 107.3 | 107.0 | 107.5 | 107.8 | 106.8 | 112.0 |

| | Hyperthermia + Placebo | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| TIME | 0 | 5 | 10 | 15 | 20 | 30 | 40 | 50 | 60 |
| AP | 84.2 | 98.0 | 96.5 | 87.3 | 91.7 | 92.0 | 85.2 | 85.3 | 91.2 |
| AT | 96.8 | 111.7 | 90.7 | 101.2 | 104.5 | 100.0 | 103.0 | 92.7 | 100.0 |
| CC | 98.7 | 96.0 | 102.5 | 101.7 | 105.7 | 115.8 | 95.0 | 93.8 | 92.7 |
| DD | 97.0 | 100.3 | 102.2 | 97.8 | 104.3 | 93.2 | 96.7 | 96.5 | 97.0 |
| JC | 96.0 | 98.0 | 91.7 | 91.8 | 91.8 | 88.3 | 87.7 | 92.2 | 90.7 |
| JK | 95.8 | 107.2 | 112.0 | 102.3 | 109.5 | 103.5 | 100.0 | 105.5 | 103.3 |
| JM | 93.5 | 102.7 | 107.2 | 107.8 | 109.0 | 102.5 | 100.7 | 99.5 | 94.3 |
| JR | 98.0 | 109.5 | 118.7 | 112.5 | 103.2 | 111.0 | 108.7 | 96.3 | 100.8 |
| MC | 94.0 | 106.5 | 112.3 | 105.7 | 106.5 | 105.5 | 98.7 | 99.7 | 90.0 |
| TT | 97.7 | 108.5 | 106.3 | 108.0 | 109.7 | 103.5 | 93.2 | 95.3 | 95.3 |
| NY | 92.3 | 106.7 | 110.8 | 110.5 | 110.8 | 101.2 | 101.5 | 97.8 | 96.0 |

| | Hyperthermia + Beta Blockade | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| TIME | 0 | 5 | 10 | 15 | 20 | 30 | 40 | 50 | 60 |
| AP | 85.0 | 97.5 | 95.2 | 96.8 | 98.3 | 90.2 | 95.7 | 95.2 | 87.8 |
| AT | 96.8 | 101.0 | 110.3 | 106.0 | 110.5 | 104.2 | 101.0 | 103.8 | 98.7 |
| CC | 104.2 | 90.2 | 96.8 | 98.5 | 95.3 | 88.0 | 91.3 | 94.2 | 89.5 |
| DD | 83.7 | 96.5 | 97.7 | 99.7 | 100.3 | 100.3 | 96.3 | 95.7 | 95.5 |
| JC | 92.2 | 97.3 | 97.3 | 93.7 | 94.5 | 86.2 | 85.3 | 88.0 | 84.8 |
| JK | 100.2 | 112.2 | 110.0 | 102.8 | 105.5 | 108.5 | 101.8 | 98.2 | 97.0 |
| JM | 98.8 | 113.3 | 109.5 | 109.2 | 107.3 | 103.3 | 100.5 | 88.2 | 95.3 |
| JR | 91.0 | 108.3 | 117.0 | 113.0 | 115.8 | 110.0 | 100.7 | 93.8 | 94.5 |
| MC | 98.3 | 103.3 | 104.8 | 104.8 | 102.5 | 103.7 | 98.2 | 99.3 | 98.3 |
| TT | 95.7 | 106.7 | 95.5 | 103.0 | 100.0 | 94.8 | 93.8 | 87.7 | 79.8 |
| NY | 89.7 | 93.5 | 99.8 | 100.2 | 102.2 | 111.7 | 113.0 | 105.3 | 108.3 |

OXYGEN CONSUMPTION (l/min)

| Subject | Normothermia + Placebo | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| TIME | 0 | 5 | 10 | 15 | 20 | 30 | 40 | 50 | 60 |
| AP | 0.240 | 2.057 | 2.139 | 2.090 | 2.240 | 2.080 | 2.015 | 2.145 | 2.184 |
| AT | 0.396 | 2.011 | 2.018 | 1.989 | 2.053 | 2.035 | 2.121 | 2.131 | 2.065 |
| CC | 0.324 | 2.268 | 2.340 | 2.351 | 2.387 | 2.502 | 2.512 | 2.404 | 2.437 |
| DD | 0.352 | 1.840 | 1.938 | 1.873 | 1.950 | 1.996 | 2.004 | 1.968 | 1.977 |
| JC | 0.552 | 2.329 | 2.422 | 2.459 | 2.478 | 2.517 | 2.579 | 2.575 | 2.633 |
| JK | 0.312 | 2.028 | 2.009 | 2.082 | 2.116 | 2.104 | 2.131 | 2.176 | 2.151 |
| JM | 0.311 | 1.998 | 2.084 | 2.090 | 2.084 | 2.033 | 2.027 | 2.109 | 2.093 |
| MC | 0.526 | 2.781 | 2.795 | 2.773 | 2.900 | 2.878 | 2.853 | 2.891 | 2.900 |
| TT | 0.288 | 1.935 | 2.035 | 2.058 | 2.070 | 2.119 | 2.173 | 2.159 | 2.181 |
| JR | 0.404 | 2.370 | 2.428 | 2.560 | 2.665 | 2.621 | 2.676 | 2.680 | 2.649 |
| NY | 0.299 | 1.706 | 1.843 | 1.856 | 1.850 | 1.901 | 1.898 | 1.903 | 1.903 |

| | Normothermia + Beta Blockade | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| TIME | 0 | 5 | 10 | 15 | 20 | 30 | 40 | 50 | 60 |
| AP | 0.282 | 2.012 | 1.963 | 1.936 | 2.005 | 2.050 | 2.137 | 2.178 | 2.054 |
| AT | 0.391 | 1.990 | 2.024 | 2.132 | 2.179 | 2.191 | 2.188 | 2.235 | 2.197 |
| CC | 0.408 | 2.236 | 2.223 | 2.249 | 2.303 | 2.313 | 2.358 | 2.303 | 2.337 |
| DD | 0.405 | 1.814 | 1.806 | 1.870 | 2.016 | 1.964 | 1.984 | 1.975 | 1.934 |
| JC | 0.463 | 2.427 | 2.414 | 2.422 | 2.427 | 2.484 | 2.590 | 2.648 | 2.716 |
| JK | 0.209 | 2.000 | 2.160 | 2.116 | 2.133 | 2.193 | 2.147 | 2.181 | 2.161 |
| JM | 0.390 | 2.035 | 2.047 | 2.077 | 2.145 | 2.123 | 2.150 | 2.207 | 2.112 |
| MC | 0.610 | 2.591 | 2.580 | 2.679 | 2.709 | 2.818 | 2.752 | 2.802 | 2.746 |
| TT | 0.289 | 2.004 | 2.129 | 2.115 | 2.154 | 2.171 | 2.232 | 2.229 | 2.186 |
| JR | 0.503 | 2.292 | 2.361 | 2.455 | 2.526 | 2.636 | 2.607 | 2.609 | 2.606 |
| NY | 0.066 | 1.720 | 1.646 | 1.626 | 1.677 | 1.585 | 1.633 | 1.704 | 1.618 |

| | Hyperthermia + Placebo | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| TIME | 0 | 5 | 10 | 15 | 20 | 30 | 40 | 50 | 60 |
| AP | 0.272 | 1.944 | 1.944 | 1.943 | 2.031 | 2.033 | 2.016 | 2.019 | 2.012 |
| AT | 0.255 | 1.963 | 1.978 | 1.996 | 2.129 | 2.102 | 2.093 | 2.119 | 2.181 |
| CC | 0.393 | 2.152 | 2.238 | 2.305 | 2.371 | 2.436 | 2.471 | 2.473 | 2.482 |
| DD | 0.225 | 1.704 | 1.808 | 1.803 | 1.906 | 1.923 | 1.938 | 1.917 | 1.924 |
| JC | 0.436 | 2.355 | 2.449 | 2.440 | 2.500 | 2.548 | 2.598 | 2.640 | 2.657 |
| JK | 0.407 | 2.086 | 2.142 | 2.105 | 2.229 | 2.132 | 2.200 | 2.316 | 2.272 |
| JM | 0.336 | 1.982 | 2.084 | 2.087 | 2.122 | 2.183 | 2.127 | 2.243 | 2.383 |
| MC | 0.700 | 2.597 | 2.735 | 2.682 | 2.842 | 2.879 | 2.957 | 2.853 | 2.891 |
| TT | 0.229 | 2.007 | 2.117 | 2.107 | 2.174 | 2.174 | 2.133 | 2.211 | 2.210 |
| JR | 0.529 | 2.339 | 2.412 | 2.514 | 2.638 | 2.648 | 2.694 | 2.728 | 2.712 |
| NY | 0.072 | 1.636 | 1.569 | 1.612 | 1.712 | 1.745 | 1.599 | 1.687 | 1.595 |

| | Hyperthermia + Beta Blockade | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| TIME | 0 | 5 | 10 | 15 | 20 | 30 | 40 | 50 | 60 |
| AP | 0.241 | 2.083 | 2.077 | 2.065 | 2.157 | 2.149 | 2.198 | 2.218 | 2.278 |
| AT | 0.379 | 1.875 | 1.880 | 1.929 | 2.023 | 2.049 | 2.164 | 2.051 | 2.020 |
| CC | 0.385 | 2.107 | 2.176 | 2.228 | 2.384 | 2.382 | 2.391 | 2.434 | 2.488 |
| DD | 0.293 | 1.772 | 1.769 | 1.867 | 1.962 | 1.921 | 1.904 | 1.906 | 1.923 |
| JC | 0.297 | 2.307 | 2.410 | 2.525 | 2.551 | 2.579 | 2.593 | 2.597 | 2.629 |
| JK | 0.342 | 1.977 | 1.955 | 2.049 | 2.163 | 2.134 | 2.167 | 2.183 | 2.213 |
| JM | 0.302 | 1.927 | 1.913 | 1.929 | 1.938 | 1.982 | 1.976 | 2.014 | 2.052 |
| MC | 0.479 | 2.589 | 2.625 | 2.648 | 2.774 | 2.745 | 2.633 | 2.775 | 2.741 |
| TT | 0.217 | 1.880 | 1.999 | 2.004 | 2.011 | 2.048 | 2.021 | 2.066 | 2.073 |
| JR | 0.474 | 2.319 | 2.383 | 2.407 | 2.519 | 2.642 | 2.602 | 2.666 | 2.693 |
| NY | 0.085 | 1.608 | 1.697 | 1.732 | 1.681 | 1.560 | 1.673 | 1.759 | 1.712 |

VENTILATION (l/min)

| Subject | Normothermia + Placebo | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| TIME | 0 | 5 | 10 | 15 | 20 | 30 | 40 | 50 | 60 |
| AP | 9.20 | 60.79 | 63.24 | 69.48 | 66.97 | 61.48 | 58.64 | 64.97 | 59.85 |
| AT | 15.35 | 57.76 | 59.82 | 57.83 | 62.22 | 61.15 | 62.71 | 61.18 | 58.87 |
| CC | 14.63 | 63.43 | 70.66 | 69.06 | 70.06 | 74.17 | 74.13 | 67.42 | 65.89 |
| DD | 13.10 | 50.21 | 55.30 | 54.63 | 55.15 | 54.92 | 55.20 | 56.74 | 53.40 |
| JC | 20.55 | 66.46 | 71.82 | 72.66 | 76.12 | 76.07 | 77.77 | 82.38 | 84.92 |
| JK | 14.32 | 58.84 | 54.66 | 56.16 | 54.78 | 62.19 | 59.72 | 57.71 | 59.23 |
| JM | 13.40 | 58.81 | 60.21 | 59.23 | 58.82 | 54.81 | 54.86 | 59.38 | 62.41 |
| MC | 25.35 | 89.36 | 89.93 | 87.32 | 96.22 | 91.70 | 93.08 | 94.37 | 90.34 |
| TT | 12.31 | 67.39 | 68.83 | 69.23 | 68.73 | 70.71 | 72.77 | 72.86 | 73.06 |
| JR | 13.85 | 61.40 | 64.63 | 69.06 | 72.64 | 70.73 | 75.74 | 75.10 | 74.41 |
| NY | 14.09 | 54.40 | 55.99 | 59.42 | 58.55 | 60.31 | 59.27 | 59.87 | 61.62 |

| | Normothermia + Beta Blockade | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| TIME | 0 | 5 | 10 | 15 | 20 | 30 | 40 | 50 | 60 |
| AP | 11.06 | 53.98 | 52.27 | 51.48 | 58.75 | 53.84 | 60.98 | 58.86 | 55.26 |
| AT | 14.21 | 61.04 | 57.99 | 66.22 | 68.73 | 67.52 | 64.52 | 65.39 | 62.07 |
| CC | 17.38 | 62.03 | 59.13 | 60.77 | 63.85 | 65.37 | 66.33 | 64.70 | 67.60 |
| DD | 14.03 | 50.42 | 47.02 | 51.04 | 52.71 | 56.15 | 53.09 | 54.21 | 57.65 |
| JC | 21.58 | 68.80 | 70.00 | 67.41 | 69.90 | 73.66 | 73.55 | 82.11 | 88.85 |
| JK | 11.49 | 50.97 | 56.69 | 57.92 | 58.24 | 63.08 | 64.85 | 62.05 | 64.59 |
| JM | 14.70 | 56.70 | 58.13 | 58.02 | 62.33 | 60.79 | 62.86 | 64.89 | 62.73 |
| MC | 25.07 | 77.50 | 74.64 | 81.83 | 84.04 | 85.48 | 85.21 | 84.30 | 79.96 |
| TT | 12.30 | 69.75 | 72.33 | 74.58 | 73.10 | 74.05 | 73.83 | 71.57 | 72.40 |
| JR | 15.75 | 57.61 | 61.87 | 61.70 | 65.07 | 69.05 | 65.24 | 62.42 | 70.82 |
| NY | 10.95 | 52.81 | 54.88 | 55.45 | 57.64 | 54.18 | 56.04 | 59.58 | 56.85 |

| | Hyperthermia + Placebo | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| TIME | 0 | 5 | 10 | 15 | 20 | 30 | 40 | 50 | 60 |
| AP | 11.75 | 56.98 | 56.06 | 60.92 | 59.73 | 57.33 | 61.57 | 61.77 | 58.99 |
| AT | 11.69 | 57.23 | 61.12 | 62.44 | 65.24 | 64.94 | 64.78 | 63.48 | 68.25 |
| CC | 15.14 | 56.87 | 62.08 | 67.31 | 71.39 | 75.54 | 77.83 | 75.75 | 77.68 |
| DD | 9.45 | 51.57 | 54.73 | 55.00 | 58.38 | 58.33 | 59.99 | 61.09 | 54.99 |
| JC | 20.41 | 68.61 | 74.98 | 75.02 | 79.17 | 79.31 | 83.64 | 86.00 | 89.21 |
| JK | 16.91 | 54.56 | 58.50 | 57.44 | 64.58 | 60.30 | 63.84 | 65.14 | 62.38 |
| JM | 15.11 | 56.74 | 60.33 | 61.64 | 61.72 | 64.44 | 61.56 | 69.62 | 88.71 |
| MC | 30.64 | 79.84 | 85.32 | 82.77 | 92.86 | 99.52 | 103.82 | 108.13 | 103.72 |
| TT | 11.02 | 70.17 | 76.52 | 75.54 | 75.58 | 75.58 | 72.49 | 87.68 | 87.68 |
| JR | 16.21 | 67.28 | 68.43 | 78.42 | 83.03 | 80.07 | 86.20 | 94.54 | 92.23 |
| NY | 11.30 | 54.36 | 55.63 | 60.27 | 62.77 | 65.57 | 60.51 | 67.19 | 65.73 |

| | Hyperthermia + Beta Blockade | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| TIME | 0 | 5 | 10 | 15 | 20 | 30 | 40 | 50 | 60 |
| AP | 11.09 | 59.73 | 63.74 | 64.69 | 67.23 | 68.20 | 71.93 | 70.18 | 74.56 |
| AT | 14.07 | 57.99 | 55.09 | 60.92 | 64.67 | 62.68 | 67.84 | 63.23 | 62.22 |
| CC | 16.57 | 55.40 | 60.05 | 64.91 | 70.62 | 68.92 | 68.51 | 69.04 | 73.79 |
| DD | 12.67 | 48.08 | 52.80 | 52.66 | 55.12 | 54.33 | 53.95 | 56.08 | 53.48 |
| JC | 14.53 | 66.25 | 70.06 | 73.33 | 77.46 | 72.73 | 77.62 | 76.11 | 81.08 |
| JK | 13.96 | 50.14 | 52.72 | 52.76 | 60.14 | 62.76 | 59.56 | 59.46 | 63.07 |
| JM | 13.01 | 55.55 | 53.80 | 55.72 | 57.35 | 58.10 | 60.01 | 63.13 | 68.00 |
| MC | 29.87 | 73.36 | 83.03 | 82.31 | 91.65 | 90.80 | 85.21 | 90.44 | 95.54 |
| TT | 10.81 | 62.45 | 61.07 | 59.69 | 62.34 | 64.09 | 61.87 | 58.86 | 68.86 |
| JR | 21.88 | 63.55 | 62.92 | 68.29 | 67.99 | 75.20 | 71.49 | 76.74 | 81.24 |
| NY | 11.83 | 50.16 | 57.12 | 57.64 | 57.77 | 58.57 | 59.53 | 62.02 | 63.78 |

RATING OF PERCEIVED EXERTION

| SUBJECT | Normothermia + Placebo | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| TIME | 5 | 10 | 15 | 20 | 30 | 40 | 50 | 60 |
| AP | 13 | 13 | 13 | 13 | 13 | 13 | 13 | 13 |
| AT | 12 | 13 | 13 | 13 | 13 | 13 | 13 | 13 |
| CC | 12 | 13 | 13 | 13 | 13 | 13 | 12 | 12 |
| DD | 12 | 13 | 14 | 14 | 15 | 15 | 16 | 15 |
| JC | 12 | 12 | 12 | 12 | 13 | 13 | 14 | 15 |
| JK | 12 | 12 | 12 | 12 | 12 | 12 | 12 | 13 |
| JM | 12 | 12 | 13 | 13 | 13 | 13 | 13 | 14 |
| MC | 12 | 12 | 12 | 12 | 13 | 13 | 13 | 14 |
| TT | 11 | 12 | 12 | 12 | 12 | 12 | 13 | 15 |
| JR | 8 | 9 | 11 | 11 | 12 | 13 | 14 | 14 |
| NY | 12 | 12 | 12 | 12.5 | 12.5 | 13 | 13 | 14 |

| | Normothermia + Beta Blockade | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| TIME | 5 | 10 | 15 | 20 | 30 | 40 | 50 | 60 |
| AP | 13 | 13 | 13 | 13 | 13 | 13 | 13 | 13 |
| AT | 13 | 13 | 13 | 13 | 13 | 14 | 14 | 14 |
| CC | 12 | 12 | 12 | 12 | 12 | 12 | 13 | 13 |
| DD | 12 | 13 | 13 | 15 | 14 | 15 | 15 | 16 |
| JC | 12 | 12 | 13 | 13 | 13 | 14 | 14 | 15 |
| JK | 12 | 12 | 12 | 12 | 12 | 12 | 13 | 14 |
| JM | 13 | 13 | 14 | 14 | 14 | 15 | 15 | 15 |
| MC | 12 | 12 | 12 | 13 | 13 | 14 | 14 | 14 |
| TT | 13 | 13 | 13 | 14 | 14 | 14 | 15 | 17 |
| JR | 8 | 9 | 11 | 12 | 12 | 12 | 13 | 13 |
| NY | 12 | 12 | 12 | 13 | 13 | 13 | 14 | 14.5 |

| | Hyperthermia + Placebo | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| TIME | 5 | 10 | 15 | 20 | 30 | 40 | 50 | 60 |
| AP | 14 | 14 | 14 | 14 | 15 | 15 | 15 | 15 |
| AT | 12.5 | 13 | 13 | 13 | 13 | 13 | 13 | 13 |
| CC | 12 | 13 | 13 | 13 | 13 | 13 | 13 | 13 |
| DD | 13 | 13 | 14 | 14 | 15 | 15 | 15 | 16 |
| JC | 12 | 12 | 13 | 13 | 14 | 15 | 17 | 18 |
| JK | 12 | 12 | 13 | 13 | 14 | 15 | 15 | 17 |
| JM | 12 | 12 | 13 | 13 | 14 | 14 | 15 | 16 |
| MC | 12 | 13 | 13 | 13 | 15 | 16 | 17 | 17 |
| TT | 12 | 12 | 13 | 13 | 14 | 16 | 17 | 17 |
| JR | 9 | 10 | 10 | 11 | 12 | 14 | 15 | 16 |
| NY | 12 | 12 | 12 | 12 | 13 | 13 | 14 | 14 |

| | Hyperthermia + Beta Blockade | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| TIME | 5 | 10 | 15 | 20 | 30 | 40 | 50 | 60 |
| AP | 14 | 14 | 15 | 16 | 16.5 | 17 | 17 | 18 |
| AT | 13 | 13 | 13 | 13 | 13 | 14 | 14 | 13 |
| CC | 13 | 13 | 13 | 13 | 13 | 14 | 14 | 14 |
| DD | 13 | 14 | 14 | 15 | 15 | 16 | 16 | 16 |
| JC | 12 | 12 | 13 | 13 | 14 | 15 | 16 | 18 |
| JK | 11 | 11 | 12 | 12 | 13 | 13 | 13 | 15 |
| JM | 13 | 13 | 13 | 13 | 13 | 14 | 14 | 15 |
| MC | 13 | 13 | 13 | 13 | 14 | 15 | 16 | 16 |
| TT | 12 | 12 | 13 | 13 | 13 | 15 | 16 | 18 |
| JR | 9 | 9 | 11 | 11 | 14 | 14 | 16 | 16 |
| NY | 12 | 13 | 13 | 13 | 14 | 15 | 16 | 17 |

FOREARM BLOOD FLOW (ml/100ml/min)

| Subject | Normothermia + Placebo | | | |
|---|---|---|---|---|
| TIME | 0 | 12 | 35 | 55 |
| AP | 1.3 | 8.1 | 11.7 | 9.4 |
| AT | 2.9 | 15.3 | 14.2 | 15.2 |
| CC | 2.9 | 11.7 | 11.9 | 11.6 |
| DD | 1.0 | 7.1 | 7.2 | 8.6 |
| JC | 1.9 | 5.8 | 7.8 | 6.9 |
| JK | 1.8 | 9.1 | 5.2 | 5.9 |
| JM | 2.1 | 5.6 | 5.6 | 5.9 |
| JR | 0.6 | 5.8 | 6.1 | 7.0 |
| MC | 1.8 | 10.1 | 11.8 | 11.8 |
| TT | 1.3 | 4.5 | 14.3 | 17.2 |
| NY | 1.1 | 5.6 | 6.7 | 6.7 |

| | Normothermia + Beta Blockade | | | |
|---|---|---|---|---|
| TIME | 0 | 12 | 35 | 55 |
| AP | 1.0 | 7.2 | 9.9 | 10.6 |
| AT | 3.7 | 12.5 | 10.5 | 18.3 |
| CC | 3.5 | 13.9 | 15.5 | 16.3 |
| DD | 0.7 | 7.3 | 9.1 | 10.8 |
| JC | 2.1 | 9.2 | 9.7 | 12.8 |
| JK | 1.9 | 9.0 | 7.7 | 6.2 |
| JM | 1.7 | 6.8 | 8.5 | 6.2 |
| JR | 2.3 | 6.7 | 8.5 | 11.7 |
| MC | 1.7 | 14.8 | 11.2 | 9.7 |
| TT | 1.2 | 4.9 | 15.4 | 17.7 |
| NY | 1.3 | 8.0 | 7.8 | 8.2 |

| | Hyperthermia + Placebo | | | |
|---|---|---|---|---|
| TIME | 0 | 12 | 35 | 55 |
| AP | 1.0 | 9.5 | 11.1 | 11.3 |
| AT | 1.7 | 16.2 | 24.9 | 19.2 |
| CC | 3.4 | 20.4 | 22.4 | 25.0 |
| DD | 1.5 | 13.9 | 18.6 | 19.7 |
| JC | 2.8 | 10.2 | 14.8 | 14.4 |
| JK | 1.1 | 12.8 | 18.6 | 14.1 |
| JM | 2.4 | 20.4 | 17.2 | 14.1 |
| JR | 2.4 | 10.9 | 8.8 | 9.8 |
| MC | 4.1 | 18.3 | 21.1 | 16.5 |
| TT | 1.3 | 16.8 | 16.7 | 16.0 |
| NY | 1.0 | 8.3 | 10.1 | 9.2 |

| | Hyperthermia + Beta Blockade | | | |
|---|---|---|---|---|
| TIME | 0 | 12 | 35 | 55 |
| AP | 1.5 | 13.5 | 15.1 | 13.2 |
| AT | 4.2 | 23.9 | 23.1 | 23.0 |
| CC | 3.4 | 18.2 | 17.2 | 18.1 |
| DD | 1.6 | 12.4 | 12.7 | 11.4 |
| JC | 2.0 | 10.0 | 11.2 | 12.6 |
| JK | 1.3 | 18.3 | 19.9 | 13.5 |
| JM | 2.0 | 9.4 | 13.1 | 11.1 |
| JR | 2.5 | 12.9 | 13.8 | 12.9 |
| MC | 4.0 | 17.2 | 20.2 | 18.6 |
| TT | 0.7 | 13.4 | 15.4 | 17.7 |
| NY | 1.0 | 10.1 | 11.5 | 7.0 |

CUTANEOUS BLOOD FLOW (arbitrary units)

| Subject | Normothermia + Placebo | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| TIME | 0 | 5 | 10 | 15 | 20 | 30 | 40 | 50 | 60 |
| AP | 24.9 | 49.9 | 71.4 | 114.0 | 100.0 | 104.7 | 99.6 | 108.0 | 102.7 |
| AT | 32.6 | 59.6 | 192.1 | 173.4 | 180.5 | 192.4 | 179.5 | 171.8 | 172.5 |
| CC | 44.4 | 68.5 | 111.5 | 130.4 | 121.4 | 125.5 | 183.1 | 160.1 | 137.1 |
| DD | 28.6 | 38.5 | 70.9 | 104.2 | 98.4 | 109.8 | 108.3 | 100.9 | 101.8 |
| JC | 23.2 | 36.3 | 84.1 | 94.1 | 94.7 | 95.5 | 100.8 | 112.3 | 138.4 |
| JK | 20.2 | 24.1 | 31.8 | 58.7 | 51.9 | 49.0 | 61.3 | 61.0 | 72.8 |
| JM | 16.6 | 31.6 | 65.0 | 71.3 | 73.1 | 73.0 | 81.3 | 67.5 | 75.5 |
| JR | 27.8 | 45.9 | 83.0 | 101.0 | 90.6 | 105.0 | 100.7 | 103.2 | 91.4 |
| MC | 22.3 | 32.6 | 81.5 | 88.7 | 86.7 | 83.1 | 79.8 | 76.3 | 77.8 |
| TT | 21.0 | 27.0 | 49.6 | 97.8 | 113.0 | 191.4 | 187.1 | 192.6 | 187.6 |

| | Normothermia + Beta Blockade | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| TIME | 0 | 5 | 10 | 15 | 20 | 30 | 40 | 50 | 60 |
| AP | 18.5 | 36.0 | 90.3 | 118.1 | 111.4 | 120.0 | 108.0 | 107.4 | 93.8 |
| AT | 30.0 | 68.3 | 164.7 | 153.6 | 155.5 | 134.5 | 143.9 | 141.4 | 141.1 |
| CC | 34.5 | 44.5 | 80.5 | 84.0 | 80.9 | 96.6 | 98.0 | 92.9 | 90.5 |
| DD | 27.7 | 29.1 | 54.8 | 68.0 | 82.9 | 81.4 | 78.8 | 87.1 | 118.6 |
| JC | 26.5 | 27.0 | 83.6 | 82.1 | 79.2 | 76.5 | 75.8 | 95.3 | 100.6 |
| JK | 18.7 | 25.9 | 36.2 | 62.7 | 57.0 | 58.1 | 69.8 | 72.1 | 69.3 |
| JM | 17.7 | 24.5 | 60.2 | 66.8 | 68.2 | 66.9 | 73.0 | 68.8 | 66.9 |
| JR | 32.9 | 59.9 | 150.2 | 175.6 | 180.7 | 170.2 | 167.2 | 165.1 | 158.3 |
| MC | 21.0 | 28.9 | 120.8 | 114.7 | 128.2 | 126.7 | 115.2 | 124.9 | 107.7 |
| TT | 19.2 | 32.3 | 49.0 | 78.4 | 100.6 | 116.3 | 140.8 | 132.9 | 118.4 |

| | Hyperthermia + Placebo | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| TIME | 0 | 5 | 10 | 15 | 20 | 30 | 40 | 50 | 60 |
| AP | 32.0 | 53.7 | 144.3 | 133.0 | 140.0 | 127.9 | 131.3 | 141.7 | 130.7 |
| AT | 46.4 | 131.7 | 184.8 | 170.5 | 205.3 | 178.0 | 172.9 | 161.8 | 171.6 |
| CC | 42.0 | 157.7 | 202.6 | 229.5 | 210.2 | 236.1 | 230.8 | 220.2 | 218.9 |
| DD | 23.9 | 26.6 | 64.2 | 69.7 | 75.5 | 83.4 | 90.1 | 89.6 | 89.0 |
| JC | 48.6 | 126.1 | 288.5 | 266.5 | 237.8 | 311.5 | 306.3 | 189.5 | 173.9 |
| JK | 12.4 | 40.9 | 97.8 | 101.2 | 100.6 | 105.9 | 130.0 | 105.9 | 103.4 |
| JM | 24.7 | 46.6 | 74.7 | 72.9 | 88.9 | 81.4 | 84.6 | 80.4 | 88.0 |
| JR | 45.9 | 183.7 | 214.8 | 202.7 | 181.0 | 190.0 | 185.0 | 161.8 | 168.1 |
| MC | 40.9 | 100.6 | 120.0 | 124.5 | 132.1 | 133.7 | 128.3 | 128.9 | 129.5 |
| TT | 29.3 | 41.7 | 82.7 | 106.6 | 141.8 | 148.0 | 144.5 | 142.0 | 176.9 |

| | Hyperthermia + Beta Blockade | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| TIME | 0 | 5 | 10 | 15 | 20 | 30 | 40 | 50 | 60 |
| AP | 17.6 | 47.5 | 75.2 | 75.0 | 80.7 | 80.0 | 90.5 | 91.4 | 95.4 |
| AT | 37.6 | 189.9 | 186.7 | 193.3 | 191.0 | 166.3 | 186.3 | 160.7 | 176.0 |
| CC | 291.8 | 346.0 | 344.1 | 302.5 | 287.4 | 246.3 | 243.5 | 237.1 | 243.9 |
| DD | 33.5 | 55.4 | 123.3 | 124.9 | 102.6 | 134.7 | 104.8 | 98.5 | 101.7 |
| JC | 38.6 | 54.0 | 115.0 | 123.4 | 126.7 | 204.7 | 225.1 | 189.5 | 173.9 |
| JK | 41.0 | 67.4 | 121.9 | 108.6 | 272.9 | 118.2 | 110.4 | 116.6 | 137.8 |
| JM | 36.1 | 76.6 | 105.0 | 123.3 | 112.3 | 93.4 | 94.3 | 125.2 | 117.8 |
| JR | 3.6 | 163.8 | 199.7 | 201.1 | 198.8 | 201.3 | 201.8 | 184.0 | 188.2 |
| MC | 36.0 | 51.1 | 104.5 | 96.2 | 118.4 | 136.6 | 158.9 | 164.6 | 176.9 |
| TT | 29.3 | 41.7 | 82.7 | 106.6 | 141.8 | 148.0 | 144.5 | 142.0 | 176.9 |

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# VITA

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